CRITICAL CARE
SELF-ASSESSMENT PROGRAM

CCSAP

2016 • BOOK 3

PAIN AND SEDATION/ SUPPORT AND PREVENTION

Series Editors
Bradley A. Boucher, Pharm.D., FCCP, FNAP, MCCM, BCPS
Curtis E. Haas, Pharm.D., FCCP, BCPS

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Director of Professional Development: Nancy M. Perrin, M.A., CAE
Associate Director of Professional Development: Wafa Y. Dahdal, Pharm.D., BCPS
Recertification Project Manager: Edward Alderman, B.S., B.A.
Medical Editor: Kimma Sheldon, Ph.D., M.A.
Information Technology Project Manager: Brent Paloutzian, A.A.S.

For ordering information or questions, write or call:
Critical Care Self-Assessment Program
American College of Clinical Pharmacy
13000 W. 87th St. Parkway
Lenexa, KS 66215-4530
Telephone: (913) 492-3311
Fax: (913) 492-4922
E-mail: accp@accp.com

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Message from the Editors

Welcome to the Critical Care Self-Assessment Program (CCSAP), a new recertification component for the Board Certified Critical Care Pharmacist. ACCP has a long tradition of offering the best products for continuing pharmacy education and pharmacotherapy specialist certification. CCSAP continues that tradition by providing the latest in evidence-based information for the critical care practitioner or clinician.

In designing this series, the primary goal was to provide updates that would improve clinical pharmacy practice and patient outcomes. The process began with a careful review of the content outline developed by the Board of Pharmacy Specialties for the Critical Care Pharmacy Specialty Certification Examination. The 2016–2018 CCSAP chapters will therefore cover the domains of clinical skills and therapeutic management; practice administration and development; and information management and education. Specific content for individual releases in this series was organized on the basis of the systems and patient-care problems that might be expected of the board certified critical care pharmacy specialist. Finally, calls went out to recruit faculty panel chairs, authors, and reviewers committed to this new specialty and to the board certification process.

The presentation of information, and its incorporation into practice, was also given careful consideration. Inside this CCSAP book, you will find user-friendly formatting as well as graphic elements such as patient-care scenarios demonstrating the application of concepts, treatment algorithms, descriptions of pivotal studies that may change practice, and summative practice points. All releases in this series are available electronically, enhancing the portability of this product. Prominent in each chapter are hyperlinks to reference sources, assessment tools, guidelines and resources, data compilers such as PubMed, and even informational videos. Our hope is that this depth of information, ease of access, and emphasis on clinical application will have an immediate and positive impact on the care of patients in the ICU and other critical care settings.

We very much appreciate the efforts of all the contributors who lent their energy and expertise to this new series.

Bradley A. Boucher and Curtis E. Haas, series editiors

Pain and Sedation I

Pain and Sedation I Panel

Series Editors:

Bradley A. Boucher, Pharm.D., FCCP, FNAP, MCCM, BCPS
Professor of Clinical Pharmacy
Associate Dean for Strategic Initiatives and Operations
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Curtis E. Haas, Pharm.D., FCCP
Director of Pharmacy
University of Rochester Medical Center
Rochester, New York

Faculty Panel Chair:

Amy L. Dzierba, Pharm.D., BCPS, BCCCP, FCCM
Critical Care Pharmacist, Medical Intensive Care Unit
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

Pain and Analgesia

Authors

Gilles L. Fraser, Pharm.D., MCCM
Clinical Pharmacy Specialist in Critical Care
Departments of Pharmacy and Critical Care
Maine Medical Center
Portland, Maine
Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts

David J. Gagnon, Pharm.D. BCCCP
Clinical Pharmacist-Critical Care
Department of Pharmacy
Maine Medical Center
Portland, Maine
Clinical Assistant Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts

Reviewers

Joseph F. Dasta, M.S., FCCP, MCCM
Professor Emeritus
Division of Pharmacy Practice and Science
The Ohio State University College of Pharmacy
Columbus, Ohio

John Carothers, Pharm.D., BCCCP, BCPS
Critical Care Clinical Pharmacist
Department of Inpatient Pharmacy
Alaska Native Medical Center
Anchorage, Alaska

Billie Bartel, Pharm.D., BCCCP
Clinical Pharmacist
Sanford Aberdeen Medical Center
Aberdeen, South Dakota

Agitation in Mechanically Ventilated ICU Patients

Author

Joshua T. Swan, Pharm.D., MPH, BCPS
Administrative Specialist 1 in Drug Information, Formulary Management, & Research
Department of Pharmacy Services
Houston Methodist Hospital
Assistant Professor of Allied Health Sciences
Institute for Academic Medicine
Houston Methodist Research Institute
Houston, Texas

Reviewers

Stephanie Mallow Corbett, Pharm.D., FCCM
Medication Quality, Performance Improvement and Safety Officer/Coach
University of Virginia Health System
Charlottesville, Virginia

Jessica M. Louie, Pharm.D., BCCCP
Assistant Professor
Department of Pharmacy Practice
West Coast University School of Pharmacy
Los Angeles, California

Nadia Ferguson-Myrthil, Pharm.D., BCPS
Clinical Pharmacy Manager for Critical Care
Department of Pharmacy
Montefiore Medical Center, Einstein Campus
Clinical Assistant Professor of Medicine
Department of Pharmacy
Albert Einstein College of Medicine
Bronx, New York

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Pain and Sedation I chapters.

Judy Cheng, Pharm.D., MPH, BCPS-AQ Cardiology
Professor of Pharmacy Practice
Department of Pharmacy Practice
MCPHS University
Clinical Pharmacy Specialist
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Mary Wun-Len Lee, Pharm.D., FCCP, BCPS
Vice President and Chief Academic Officer
Pharmacy and Optometry Education
Midwestern University
Professor of Pharmacy Practice
Midwestern University
Chicago College of Pharmacy
Downers Grove, Illinois

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Consultancies: Stephanie Mallow Corbett (American College of Critical Care Medicine); Joseph F. Dasta (Janssen Scientific Affairs, LLC., Phillips-VISICU, The Medicines Company, AcelRx, Otsuka America Pharmaceuticals, Mallinckrodt, Pacira); John W. Devlin (SCCM, Vizient); Joshua T. Swan (Ablynx)

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(202) 429-7591

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Pain and Analgesia

By Gilles L. Fraser, Pharm.D., MCCM; and David J. Gagnon, Pharm.D., BCCCP

Reviewed by Joseph F. Dasta, M.S., FCCP, MCCM; John Carothers, Pharm.D., BCCCP, BCPS; and Billie Bartel, Pharm.D., BCCCP

LEARNING OBJECTIVES

1. Apply knowledge of the incidence, etiologies, and assessment of pain to the treatment of critically ill patients.
2. Develop evidence-based pain management strategies that include both nonpharmacologic and pharmacologic interventions and that account for transitions of care.
3. Design a pain control strategy for unique patient populations.
4. Evaluate short- and long-term outcomes associated with pain management, and develop methods to improve quality of care.

ABBREVIATIONS IN THIS CHAPTER

BPS	Behavioral Pain Scale
CPOT	Critical-Care Pain Observation Tool
GABA	γ-Aminobutyric acid
ICP	Intracranial pressure
NMDA	*N*-methyl-D-aspartate
NRS	Numeric Rating Scale
OIH	Opioid-induced hyperalgesia
PAD	Pain, agitation, and delirium
PTSD	Posttraumatic stress disorder

Table of other common abbreviations.

INTRODUCTION

The clinical approach to pain management in the ICU has evolved over the past few decades because of new medications, administration methods, assessment tools, and a paradigm shift using analgosedation as an initial intervention for the management of pain and agitation. Despite these advances, most ICU patients experience moderate to severe pain, which is consistently identified as one of the most troublesome memories of survivors of critical illness. Among the many reasons for this are an underappreciation of the problem, given that many patients cannot verbalize their analgesic needs, and an inability of caregivers to recognize the degree of discomfort imposed by routine ICU care. Unrelieved pain is associated with both short- and long-term physical and psychological consequences and should be the focus of evidence-based assessment, treatment, and prevention.

Pain management is extremely complex because pain presents in different ways (e.g., acute, chronic, acute on chronic), develops from different sources (e.g., somatic, visceral, neuropathic, psychogenic), and is perceived and tolerated in a highly variable manner. Add in features of the critically ill population (e.g., immobility, impaired communication, altered mental status, sleep deprivation, mechanical ventilation, procedures and interventions), and the issue becomes overwhelming without a standardized approach.

This chapter discusses these challenges and others associated with analgosedation in the critically ill population. The focus is on ICU pain as a single entity, but it should be

understood that pain, agitation, and delirium (PAD) are interrelated and can interfere with many important aspects of ICU care, including early mobility, sleep, and overall recovery.

Physiology, Etiology, and Causes

Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 1979). Accordingly, pain is a multidimensional issue with both emotional and physical components that are characterized as pain distress and pain severity, respectively.

Nociception represents the process of detecting, transmitting, and processing noxious stimuli caused by chemical, thermal, or mechanical insults. Noxious stimuli initiate nerve impulses (transduction) mediated by the intracellular release of inflammatory substances (e.g., substance P, bradykinin, histamine, prostaglandins, serotonin). These nerve impulses travel to the dorsal horn of the spinal cord, where they mediate the release of both excitatory (i.e., glutamate or aspartate) and inhibitory (i.e., γ-aminobutyric acid [GABA]) neurotransmitters in the thalamus and midbrain. The interplay between these neurotransmitters helps define an individual's response to noxious stimuli (perception). Modulation of the pain signal occurs with the release of endorphins and enkephalins (Reardon 2015).

There are at least three types of pain. Somatic nociception is associated with peripheral tissue injury and is characterized by sharp, stabbing, or dull pain that can be localized. Visceral nociception is associated with organ injury, is typically difficult to localize, and is characterized in vague terms such as *cramping*. Neuropathic pain originates from disorders of the central and peripheral nervous systems. Peripheral neuropathic pain is caused by neuronal lesions related to trauma, infections (e.g., postherpetic neuralgia), and ischemia (e.g., diabetes, vascular disease). Central neuropathic pain results from diseases of the CNS, spinal cord injury, or demyelinating diseases (e.g., multiple sclerosis) (Reardon 2015).

Most ICU patients experience moderate to severe pain from sources such as acute and chronic illness, surgery, trauma, burn injuries, pancreatitis, cancer, comorbidities (e.g., arthritis, chronic pain syndromes), immobility, invasive medical and monitoring devices, and routine ICU care (e.g., procedures) (Box 1-1). In addition, many conditions (e.g., diabetes mellitus, Guillain-Barré syndrome) can lead to neuropathic pain (Sigakis 2015).

Although procedures are known to be common sources of ICU pain, preemptive analgesia is administered less than 25% of the time. A landmark 2014 study of 3851 ICU patients who underwent 4812 procedures measured associated pain intensity. All evaluated procedures were associated with some degree of pain, and three (i.e., chest tube removal, wound drain removal, and arterial line insertion) led to pain intensity more than double from baseline. Of interest, patients perceived procedures performed by nurses as less painful than those done by other caregivers and physicians. Investigators hypothesize that anxiety and its associated increase in pain perception were limited because nurses provide reassurance, compassion, and pre-procedural education and often include family members (Puntillo 2014).

Pain Assessment

Management of ICU pain starts with a careful assessment of its source, duration, and severity. This is difficult in the ICU

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of medications commonly used for analgesia
- Adverse drug effects of analgesic agents
- Pharmacologic properties of opioids

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Society of Critical Care Medicine. ICU Liberation [homepage on the Internet].
- Joint Commission. Sentinel Event Alert Issue 49: safe use of opioids in hospitals.
- Joint Commission. Pain management [homepage on the Internet].
- National Institute on Health and Care Excellence. Opioid use in renal impairment.
- American Pain Society. Guidelines on the management of postoperative pain. J Pain 2016;17:131-57.
- ICU Liberation. Assess, Prevent, and Manage Pain [homepage on the Internet].

Box 1-1. Routine ICU Procedures Associated with Pain

- Turning and repositioning
- Obtaining peripheral blood or intravenous and arterial line insertions
- Endotracheal and tracheal suctioning
- Chest tube and wound drain placement or removal
- Mobilization and respiratory exercises
- Wound care

Information from Puntillo KA, Max A, Timsit JF, et al. Determinants of procedural pain intensity in the ICU. Am J Respir Crit Care Med 2014;189:39-47.

because patients are often unable to communicate or have cognitive impairment. Recent European data suggest that although 80% of ICUs routinely monitor pain using a validated pain assessment tool when the patient is able to self-report, only 30% use validated behavioral pain assessment tools for patients unable to communicate (Luetz 2014). The PAD guidelines identify pain assessment as an area where gaps in practice exist and suggest that assessments be performed and documented at least four times per nursing shift, before and after analgesia has been administered, and with any change in patient condition (Barr 2013). Of importance, systematic assessments of pain can reduce its frequency by 33% and reduce sedative use, mechanical ventilation dependency, ICU length of stay, and mortality (Joffe 2013; Payen 2009).

Self-report

Individual pain tolerance is widely appreciated, but cultural differences may not be. For example, patients of Hebrew, Chinese, and Japanese origins have very few expressions for pain in their vernacular, which may impair their ability to provide detailed descriptions of pain. In contrast, the English language includes 16 categories of pain described by at least 64 words (Puntillo 2009). Self-reporting, therefore, remains the gold standard for pain assessment in the critically ill population. To self-report, a patient cannot be deeply sedated and must be able to interact in a meaningful way with caregivers.

The Numeric Rating Scale Visual (NRS-V) may be the easiest assessment tool to use; moreover, it offers the best negative predictive value and likely represents the most widely used metric (Gelinas 2014). The cutoff score for significant pain using the NRS-V is greater than 3.

The presence of an endotracheal tube or a tracheostomy should not preclude pain assessments. Different methods of communication beyond vocalization can and should be used (e.g., tight eye squeezing, blinking, finger gestures). A laminated tool with a numeric format that includes body locations where pain is felt, together with words to describe the qualitative nature of pain (e.g., sharp, aching, burning), is often beneficial.

Vital Signs

Vital signs are not consistent indicators of ICU pain; have not been correlated with patient self-reporting or validated pain assessment tools; and can change in response to fear, anxiety, or other stressors. Acute changes in vital signs, however, can be used as cues to perform an evaluation with a validated tool (e.g., self-report or behavioral-based pain assessments) (Barr 2013). Overall, vital signs should not be used as the sole indicator of pain.

Behavioral Pain Scales

In an effort to improve pain evaluations in noncommunicative patients, assessment tools based on behavioral pain indicators (e.g., facial expression, body movement, muscle movements or tension, compliance with the ventilator) have been developed and tested for reliability and validity. These tools represent a significant advancement in the management of ICU pain, but they should only be used when patient self-report is impossible and when motor function is intact. The PAD guidelines recommend the Critical-Care Pain Observation Tool (CPOT) and the Behavioral Pain Scale (BPS) for use in noncommunicative patients. These tools have common features, but they are not useful for measuring pain intensity and cannot discriminate between pain types. Thresholds to identify significant pain in patients are greater than 2 for CPOT and greater than 5 for BPS.

Surrogate Reporting

A patient's family members often serve as advocates, especially when they perceive that their loved one is experiencing pain. Compared with patient self-report, surrogates correctly identify the presence of pain 74% of the time and the severity of pain 53% of the time, with a tendency to overestimate pain intensity (Desbiens 2000). Although consideration of family concerns is important, it remains the responsibility of health care providers to evaluate pain and the need for interventions.

Agreement of pain severity between nurse report and patient report is around 75%. Although this may seem good, nurses underestimate significant pain (NRS greater than 3) almost 60% of the time (Ahlers 2008). These data emphasize the importance of providing light sedation to allow patients to accurately describe their analgesic needs. These data also support the contention that pain assessments should be combined with several sources of information when patient self-report is not possible.

Analgesic Trial

Occasionally, despite the use of evaluative strategies, there is uncertainty about whether a patient is experiencing pain. When this occurs, it is reasonable to offer an analgesic trial followed by observation. If patient behaviors seem to respond to an analgesic trial, consideration of continued administration is indicated. If there is no response to analgesia, other causes of the patient's behaviors should be explored (Herr 2006).

Incidence of Pain

Most patients experience moderate to severe pain during their ICU stay, with the incidence varying according to patient condition and exposure to procedures. Pain even occurs at rest and is moderate to severe in about 50% of patients in both surgical and medical ICUs. Of interest, the source of the pain is different between these two groups, with surgical patients identifying pain at the site of injury and medical patients usually having back and limb pain (Robleda 2016; Chanques 2007).

Relevance: Acute and Long-term Physical and Psychological Consequences

The stress response from painful stimuli activates the autonomic nervous system, causing the release of catecholamines and stress hormones (e.g., glucagon, cortisol),

which can result in vasoconstriction and interfere with tissue perfusion and oxygen delivery. These factors may lead to hypercatabolic states, tachypnea, tachycardia, increased oxygen demand, ischemic injury, impaired wound healing and response to infections, and hyperglycemia (Sigakis 2015).

Unrelieved pain is the most traumatic memory for ICU patients. Pain also interferes with sleep, may hinder effective pulmonary toilet (coughing, deep breathing), impedes mobility and physical therapy efforts, and, if it persists, may lead to long-term issues such as chronic pain, reduced quality of life, and development of post-traumatic stress disorder (PTSD) (Sigakis 2015). However, therapeutic options available for pain management are associated with adverse events that involve the CNS, GI, and pulmonary function. All of these types of pain significantly affect patient outcomes.

MANAGEMENT

Therapeutic Goals, Documentation, and Response

The primary goal of pain management is to acutely provide patient comfort and safety; secondary goals are to prevent the immediate and long-term complications of pain. The complexity of pain management mandates a comprehensive systematic multidisciplinary approach. Pain assessments should be routinely performed and documented (at least four times per nursing shift and within 30 minutes of administering pain-relieving interventions), together with simultaneous efforts to mitigate many of the factors that initiate, sustain, or heighten the awareness of pain. Efforts should include preemptive strategies initiated before painful procedures, identification of outpatient issues such as chronic pain or history of substance abuse and tolerance with a low threshold to restart medications, if appropriate.

Pain management strategies should also be based on patient-focused treatment goals by selecting pharmacologic or nonpharmacologic interventions that consider the desired onset and duration of effect, organ dysfunction, prior response to therapy, and potential for significant drug interactions or adverse events. The exact level of pain relief should be patient-specific because some patients prefer to tolerate a degree of pain in exchange for a clearer sensorium.

Intubation and the provision of sedation offer challenges for patient-to-caregiver communication of analgesic goals, but these is not insurmountable as long as the patient is wakeful and able to use nonverbal communication tools (e.g., note writing, finger-to-word pointing). Comprehensive pain management strategies should include prevention and aggressive management of adverse drug events. Examples include initiating bowel regimens for most patients treated with opioids and providing a tapered dosing schedule for de-escalation of therapy to avoid withdrawal.

Daily interdisciplinary discussions at the bedside should address pain assessment, response to therapy, and complications encountered. Unfortunately, barriers to effective pain management can make this approach difficult to implement. A comprehensive educational approach is recommended to enhance caregiver understanding of the benefits and burdens of pharmacologic pain management, with special emphasis on patient assessment for drug choice, dose titration, and adverse drug reactions.

Barriers to Effective Pain Management

The three primary barriers to effective pain management can be characterized as provider, health care system, and patient based. Caregivers often have an underappreciation of the short- and long-term consequences of unrelieved pain and therefore relegate pain management to a lower priority. In addition, caregivers may not fully understand the extent of pain that ICU patients have and therefore the importance of frequent assessment. A survey of 800 Canadian ICU nurses showed that only 50% were aware of the existence of guidelines for ICU pain management, and even fewer targeted their administration of analgesics using a pain assessment tool (Rose 2012). These data are consistent with a multicenter observational study that found that pain assessment tools were used for only 28% of mechanically ventilated patients, and that analgesia was provided without pain assessment in most patients (Payen 2007). Caregiver personal and cultural biases may influence pain management as well, especially if they have strongly held views about the potential for opioid overuse (e.g., stereotyping or bias based on demographics such as sex, race, history of substance abuse) and drug-seeking behaviors.

The health care system may play a role in suboptimal pain management by not mandating quality improvement processes or not insisting on caregiver responsibility and accountability for pain relief. Even the structure of the provision of care may interfere with pain management such as the absence of a multidisciplinary standardized approach or established protocols. All of these can easily be exacerbated by issues related to inadequate nurse staffing.

Patients may represent significant barriers to pain management; they may accept pain as an inevitable part of illness, or not vocalize the extent of their pain as a means of avoiding adverse drug events. It has even been suggested that patients fear the consequences of reporting pain to a caregiver who may have a stronger sense of bias than empathy (Sigakis 2015; Topolovec-Vranic 2010; Pasero 2009).

Prevention Including Preprocedural Interventions

Data suggest that less than one-half of patients are assessed for pain while undergoing a potentially painful procedure, and less than one-fourth actually receive procedural pain treatment (Payen 2009). The PAD guidelines offer a strong recommendation for the use of preemptive pain control for patients before the removal of chest tubes and a weak recommendation for a similar strategy for other potentially painful procedures.

A recent randomized placebo-controlled trial showed that the use of fentanyl (1–1.5 mcg/kg per dose) before turning in a mixed ICU population of ventilated patients reduced the incidence of pain (as measured by a BPS score greater than 3) by 20%, with a number needed to treat of 5 (Robleda 2016). The authors emphasize the need for caution and careful patient selection, because 10% of patients treated with these aggressive doses of fentanyl experienced respiratory depression.

Nonpharmacologic Approaches to Pain Management

At least 33 nonpharmacologic interventions have been used for pain management in the ICU, but only three (i.e., music, deep breathing, and ice therapy) have been studied; all produced conflicting results (Joffe 2013; Gelinas 2012). Despite these uncertainties, preemptive interventions for known painful procedures should be provided because they are low cost and low risk and have the potential to complement pharmacologic options as part of a multimodal approach to analgesia (Barr 2013; Czarnecki 2011).

Pharmacologic Strategies

The choice of analgesic agent depends on a variety of patient factors, including the type, duration, and severity of pain; hemodynamic status; prior response or tolerance to therapy; presence of organ dysfunction and other comorbidities; potential for harmful drug interactions and adverse drug events; and the required onset and duration of pain relief. The route of administration of analgesia is an important consideration as well. Intravenous administration is generally preferred in the ICU because it provides rapid pain relief and because the GI tract is often not accessible or fully functional. Intermittent intravenous administration is indicated for pain caused by predictable or short-lived noxious stimuli, whereas continuous infusions are appropriate for conditions associated with sustained pain. Patient-controlled analgesia (PCA) allows selected patients control over their pain and its management, but it requires wakefulness and intact motor activity. Of importance, the use of PCA does not absolve the caregiver from assessing pain and the results of treatment. Regional or neuraxial strategies may be useful in the settings of thoracic, abdominal, vascular, and orthopedic surgery.

Multimodal interventions are well established in non-ICU settings because they provide different mechanisms of action and promise to improve analgesia while limiting exposure to opioids. Unfortunately, however, data that are specific to treating nonneuropathic ICU pain are very limited. Nevertheless, the PAD guidelines offer a conditional recommendation for the consideration of non-opioids to be administered in addition to standard opioid therapy.

In addition, an analgesia-first or analgosedation approach has been advocated because surveys show that unrelieved pain remains a significant issue for most ICU patients (Barr 2013). The analgesia-first approach provides sedating medication only after aggressive analgesic approaches have been initiated. This strategy obviates the need for prototypical sedatives in 25%–50% of patients and avoids their often significant associated adverse drug events. Outcomes resulting from an analgesia-first approach include adequate pain relief, as well as less time on the ventilator, and decreases in the ICU and hospital lengths of stay (Strom 2010).

Analgosedation is not indicated in patients with agitation that is related to drug or substance withdrawal (except opioids), drug-induced agitation (serotonin syndrome, neuroleptic malignant syndrome, or encephalopathy), or any agitation associated with a clear and reversible etiology. The general application of an analgosedation approach in the United States should be tempered by an appreciation that almost all data supporting this approach were generated in Europe, where 1:1 nurse-to-patient ratios were common and sitters were available. Furthermore, data on the influence of analgosedation on outcomes such as delirium, pneumonia, mortality, and long-term cognitive impairment are not yet available.

Opioids

Opioids are the mainstay for the treatment and prevention of pain in the ICU because they are familiar to prescribers, offer reliable analgesia, have desirable pharmacodynamic activity, and can be administered using a variety of administration routes (e.g., enteral, rectal, topical, intramuscular, intravenous, epidural). Opiates have been used for thousands of years to treat pain and "ease the harshness of life" (Chu 2008).

Opioids stimulate μ-opioid receptors, a subtype of G protein–coupled receptors that inhibit the release of inflammatory and excitatory mediators and interfere with the propagation of nerve signals, ultimately to dampen the excitability of nociceptors. They also activate N-methyl-d-aspartate (NMDA) receptors, which may lead to stimulation of nociceptors and development of tolerance. When administered in equianalgesic doses, the opioids have similar efficacy and similar non-cardiovascular adverse effects, including tolerance, constipation, suppression of cough reflexes, and respiratory depression.

Fentanyl

Fentanyl is one of the most widely used opioids in the critically ill population because it has a rapid onset of action and is readily titratable. This synthetic opioid is largely metabolized by CYP3A4. Because it is a substrate for this enzyme system, fentanyl may interact with inhibitors such as the azole antifungals, macrolides, protease inhibitors, and nondihydropyridine calcium channel blockers, as well as inducers such as barbiturates, rifampin, and carbamazepine. In addition, fentanyl competes with midazolam for clearance by CYP3A4 and reduces its clearance.

Some tertiary sources suggest that fentanyl doses should be adjusted in the setting of kidney disease. This recommendation is based on data from a handful of patients and has

no biological plausibility because only 10% of fentanyl is excreted unchanged by the kidney, and there are no active metabolites. More recent studies of a mixed critically ill population suggest that the pharmacokinetics of fentanyl are not significantly affected by renal dysfunction, though they are strongly influenced by hepatic disease, heart failure, and body mass (Choi 2016).

Fentanyl, which has 5-hydroxytryptamine 1A agonist properties, has been associated with serotonin syndrome, but the clinical significance of this is uncertain because the data are based largely on animal studies and a few case reports in humans when fentanyl had been used in combination with other agents with known serotonergic activity (Atkinson 2015). A recent retrospective single-center review evaluated the incidence of serotonin syndrome in 4500 patients treated with the combination of fentanyl and serotonergic agents from January 2012 to December 2013. Four patients (0.09%) met the criteria for serotonin syndrome; three received fentanyl patch therapy, and one received intravenous fentanyl. The incidence of serotonin syndrome in the control group (those treated with a serotonergic agent but without concomitant fentanyl) was significantly lower at 0.005% ($p<0.01$) (Koury 2015). These findings suggest that fentanyl contributes to the occurrence of serotonin syndrome, but the incidence of this adverse event is quite small. In addition, a March 2016 FDA drug safety communication warns of the risk of serotonin syndrome in patients receiving opioids, especially fentanyl, oxycodone, and methadone in conjunction with serotonergic medications.

Morphine

Morphine administration is largely limited in the ICU to traditional uses: for the treatment of dyspnea, for the treatment of myocardial infarctions for its preload reducing properties, and in the setting of palliative care because of the potential for accumulation of active metabolites in patients with kidney dysfunction, as well as its ability to cause histamine release, which may result in venodilation and bronchospasm.

Hydromorphone

Hydromorphone is a semisynthetic opioid derived from morphine. Issues with this drug stem from an underappreciation of its potency (about 6.5 times that of morphine) and resultant dosing errors; its relatively long half-life (2–3 hours), limiting easy infusion titration; and the accumulation of a potentially neurotoxic metabolite (hydromorphone-3-glucuronide) with large doses or in renal disease (Gagnon 2015).

Hydromorphone can be used to provide analgesia for patients who do not respond to high doses of other opioids. This strategy is known as opioid rotation, and supporting data are largely derived from the oncology literature. A trial of 1–2 mg of intravenous hydromorphone can be used and continued if the patient responds favorably.

Methadone

Methadone is a unique opioid because it has μ-opioid receptor agonist and NMDA receptor antagonist properties. Methadone has a complex pharmacokinetic profile: its half-life varies from 15 to 60 hours and depends on hepatic metabolism and the presence of interacting substances (Chou 2014). These factors make dose titration difficult. It has been suggested that, when methadone is used to treat chronic pain patients with opioid tolerance or who are switching from an alternative opioid, initial daily dosages should not exceed 30–40 mg, and dose titration should not exceed 10 mg daily at 5- to 7-day intervals (Chou 2014). Reasons for this caution include concerns for drug accumulation and its consequences on mental status, respiratory drive, and QTc prolongation. Recent data suggest that methadone represents the second most common cause of drug-induced ventricular dysrhythmias after dofetilide (Chou 2014). The American Pain Society practice guideline for the use of methadone suggests an ECG for most patients before initiating methadone treatment and avoidance of this agent in patients with a QTc of 500 milliseconds or greater. It is important to maintain serum potassium and magnesium in normal ranges and be mindful of the administration of other QTc-prolonging drugs. Follow-up ECGs are based on clinical context. An ECG should be performed 2–4 weeks after methadone initiation or significant dose increases for patients with risk factors for QTc prolongation, any prior ECG that showed QTc prolongation, and in those with a history of syncope. All patients should have their ECGs checked when the methadone dose reaches 30–40 mg daily and again at 100 mg daily. Finally, ECGs should be performed for all patients with new risk factors for QTc prolongation or for those who have developed arrhythmias.

The PAD guidelines offer no equianalgesic dose for methadone because it depends on the dose of the comparator opioid. In addition, the PAD guidelines offer no firm guidance on the relative potency of enteral versus intravenous administration because enteral bioavailability data are sparse and confidence intervals are wide.

Despite these potential drawbacks, methadone offers potential advantages because it may restore analgesia in patients who have become tolerant to standard opioids or when hyperalgesia is suspected. It has also been used to facilitate the discontinuation of continuous infusion opioids (Al-Qadheeb 2012), which may result in faster liberation from mechanical ventilation (Wanzuita 2012). The impact of methadone on other ICU outcomes such as length of stay and time dependent on mechanical ventilation has not yet been defined.

Remifentanil

Remifentanil is an ultra–short-acting synthetic opioid (half-life 3–10 minutes), which may offer an advantage for patients requiring frequent neurologic evaluations. It is metabolized

by nonspecific plasma esterases to inactive metabolites. It is expensive and can be associated with adverse events involving drug administration. For example, it is vital that the pharmacist and nurse work closely to avoid disruptions in therapy that might result in resurgence of pain or even withdrawal when delays in replenishing intravenous infusions occur. Hyperalgesia, which is thought to be mediated by NMDA receptor activation, has been reported with remifentanil in the perioperative setting, but not in ICU patients. Nonetheless, the potential for hyperalgesia should be anticipated with consideration of adding concurrent acetaminophen, dexmedetomidine, and ketamine to potentially mitigate this issue (Joffe 2013).

Buprenorphine

Buprenorphine is a partial μ-opioid receptor agonist with antagonist properties at the *κ*-opioid receptor with a mean half-life of 36 hours. It is available as a single agent or in combination with naloxone and is increasingly used for patients with opioid dependence and chronic pain. Buprenorphine-treated patients admitted to the ICU represent a challenge for the management of acute pain. Higher doses of standard opioids may be required for buprenorphine-treated patients to overcome the antagonist activity of the drug (Alford 2006).

Tramadol

Tramadol is an oral synthetic opioid that affects pain relief through weak μ-opioid receptor activity, serotonin release, inhibition of norepinephrine reuptake, and NMDA antagonist properties. It is converted in the liver to an active metabolite, *O*-desmethyltramadol, which is a μ-opioid agonist. Tramadol may produce less respiratory depression than typical opioids, but it is infrequently used because it is not very potent; moreover, it reduces the seizure threshold and may be associated with serotonin syndrome.

Non-opioid Analgesics

A summary of the pharmacologic properties and dosing of non-opioid analgesics used in the critically ill population is available on the ICU Liberation website.

Acetaminophen

Acetaminophen is a central cyclo-oxygenase inhibitor that consistently decreases opioid requirements by as much as 20% when used in a multimodal capacity, but the clinical correlation of a reduction in opioid-related adverse events is not clearly defined (Oyler 2015; Joffe 2013). In contrast, ICU data for enteral or intravenous acetaminophen are limited. A small double-blind placebo-controlled study evaluated the effects of intravenous acetaminophen in 40 postoperative ICU patients. Those receiving intravenous acetaminophen required 60% less opioid in the form of meperidine, were extubated quicker, had less pain (as measured by BPS and the visual analog scale), and experienced less nausea and vomiting (Memis 2010). The clinical and economic benefits of intravenous acetaminophen in the ICU setting have not been established, but it seems reasonable to consider this mode of administration for short-term use in patients until they can tolerate enteral medications.

Acetaminophen has a remarkable safety profile, but it should be used with caution and in lower doses in patients who abuse ethanol, have liver disease, or have malnutrition. Of interest, the rate of nausea with the intravenous formulation is 30%. The maximal total daily dose by any route of administration is 4000 mg.

Nonsteroidal Anti-inflammatory Drugs

These agents exert their analgesic properties principally by inhibiting the enzyme cyclo-oxygenase, resulting in a reduction in the synthesis of mediators of the acute inflammatory response, including prostaglandin synthesis in the spinal cord. All NSAIDs are similar in efficacy and adverse events; thus, choice of agent can be based on local preference and costs. These agents offer analgesia that is equivalent to acetaminophen (Joffe 2013), but their adverse effect profile mandates cautious use in patients at risk of bleeding, in those with kidney disease, and in those concomitantly using diuretics. In addition, NSAIDs may not be indicated in the trauma population because their use is associated with impaired bone fracture healing (Oyler 2015).

Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist that blocks the effects of glutamate release. Ketamine offers a clinical advantage in patients with asthma because it provides bronchodilatory effects, relieves pain unresponsive to opioids (because it is a NMDA antagonist), and improves hypotension (through endogenous catecholamine release).

Most published ketamine data are in the setting of non-ICU non-neuropathic pain, where adequate pain control was achieved with a reduction in opioid requirements and their associated adverse effects (Joffe 2013). Although there is enthusiasm for the use of ketamine infusions in the ICU, high-quality data are sparse. A recent systematic review identified one ICU-based placebo-controlled trial published in 2003 that evaluated ketamine as an opioid-sparing agent after major abdominal surgery. Morphine was administered by PCA. No other sedatives or analgesics were used. Cumulative morphine exposure was significantly less in the ketamine group (58 mg) than in placebo (80 mg) ($p<0.05$). All other measured outcomes, including confusion and hallucinations, were similar (Patanwala 2015). However, these data may not be generalizable to more severely ill patients who cannot manage their own analgesic needs.

This systematic review also identified four randomized controlled trials that compared cerebral perfusion and intracranial pressures (ICPs) in ketamine- versus opioid-treated patients with brain injury and found no between-group

differences. These limited data support further study of ketamine in this patient population (Patanwala 2015).

One randomized trial evaluated ketamine versus sufentanil in 25 patients with catecholamine-dependent heart failure receiving midazolam sedation. Hemodynamic monitoring using a pulmonary artery catheter showed that ketamine was associated with a 21% decrease in cardiac index, a 20% increase in pulmonary capillary wedge pressure, and a 38% increase in systemic vascular resistance (Patanwala 2015). Ketamine should be avoided in this population until the risk is further defined by a well-powered trial.

Adverse effects of ketamine include hypertension, diplopia, nystagmus, and nausea and vomiting. The neuropsychiatric adverse effects of ketamine on discontinuation (emergence phenomenon) seem to occur infrequently with the doses that are typically used in the ICU (less than 0.5 mg/kg/hour) and these effects may be blunted by the administration of benzodiazepines. However, data on the sustained use of ketamine in adults are limited, and the potential for neurotoxicity should temper enthusiasm until long-term exposure has shown a reasonable safety profile (Soriano 2012).

The ICU Liberation website lists pharmacokinetic and pharmacodynamic parameters on ketamine, as well as guidance on dosing.

Dexmedetomidine and Clonidine

The mechanism for pain modulation by these agents is unknown, but it may be related to α_2-receptor agonism in the substantia gelatinosa in the dorsal horn of the spinal column inhibiting somatic pain. These agents provide "cooperative" sedation without affecting respiratory drive, and data suggest that they are opioid sparing as well (Oyler 2015). Clonidine and dexmedetomidine are similar, but they can be distinguished by their degree of α_2-receptor specificity (dexmedetomidine has more), administration route (dexmedetomidine is the only intravenous α_2-receptor agent available in the United States), and cost. Cost is a significant limitation for dexmedetomidine, but this may be overcome by rapid transition to enteral clonidine in selected patients (Gagnon 2015). Both agents may cause central sympatholysis by blocking the release of norepinephrine and lead to bradycardia and hypotension.

Lidocaine

Lidocaine is widely used as a local anesthetic, for regional anesthesia, and for nerve blocks, but it is also an effective analgesic when administered intravenously. Lidocaine analgesia is mediated by sodium channel blockade and inhibition of both G protein–coupled receptors and NMDA receptors. Recent systematic reviews have described ICU-relevant data involving perioperative lidocaine infusions (Vigneault 2011; McCarthy 2010). Data in abdominal surgery suggest that lidocaine use is associated with lower pain scores, less opioid exposure, better GI function, and a reduction in hospital length of stay.

The approach to dosing has been remarkably inconsistent, with 1–2 mg/kg loading doses commonly used and sometimes followed by a continuous infusion of less than 3 mg/kg/hour for a variable duration. Serum concentrations, when measured, have consistently been less than 5 mcg/mL, and documented toxicity has been limited to hemodynamically stable arrhythmias and bradycardia (McCarthy 2010). More study is needed to define the benefits and burdens of intravenous lidocaine in ICU patients. Intravenous lidocaine should be avoided in patients with arrhythmias, sinus bradycardia, heart block, heart failure, and coronary artery disease (Adam 2015).

Lidocaine is also available for topical use as a 5% patch. This formulation may be useful as an adjunct to standard opioid therapy in the management of pain related to rib fractures (Oyler 2015). In addition, topical lidocaine administration can limit pain perception before the administration of subcutaneous lidocaine when used to facilitate invasive procedures (Wendlandt 2013).

Anticonvulsants: Gabapentin, Pregabalin, Carbamazepine

Gabapentin and pregabalin are structurally related to GABA and modulate pain response by decreasing intracellular calcium influx, which in turn decreases the release of glutamate and substance P (Oyler 2015). Carbamazepine treats pain by inhibiting sodium channels. Data for the ICU are limited to neuropathic pain associated with Guillain-Barré syndrome, where the use of gabapentin and carbamazepine was associated with greater pain relief in conjunction with fentanyl than with placebo (Barr 2013). The gabapentinoids, which are renally eliminated, require dose adjustment in the setting of kidney disease, whereas carbamazepine is noted for its ability to induce hepatic enzymes, leading to significant drug interactions.

Regional Anesthesia

Regional anesthesia is an established effective means of pain control. This strategy promises to avoid respiratory complications, allow less sedation, promote greater meaningful patient interactions, facilitate early mobility efforts, and improve GI function; however, ICU-specific data are sparse. The use of indwelling catheters has limitations dictated by the expertise of available personnel and by patient-specific relative contraindications (e.g., spinal cord injury, acute neurologic injury, coagulopathy, infections). Local anesthesia can result in high systemic serum concentrations and lead to toxicity involving the heart and CNS. The latter risk is called LAST (local anesthetic systemic toxicity), and recognition of it may be compromised in some ICU patients because of their level of sedation and comorbidities (Stundner 2012). Furthermore, epidural anesthetics are associated with hypotension.

Epidural analgesia is probably the regional anesthetic strategy most often used in the critically ill population, and

thoracic epidural anesthesia is recommended for postoperative pain management after abdominal surgery and in trauma patients with rib fractures. This technique for chest trauma patients improves lung mechanics, which may result in a lower incidence of pneumonias and a shorter duration on mechanical ventilation, but it has been associated with an increased risk of hypotension (Barr 2013). A recent systematic review of regional anesthesia and analgesia in the critically ill population informs the topic and emphasizes the lack of ICU-specific data and the need for further research to define the risks and benefits of these techniques (Stundner 2012).

Adverse Drug Events of ICU Analgesia; Focus on Opioids

Opioid-associated adverse drug events are very common and account for as much as 16% of all inpatient adverse drug reactions. These include respiratory and CNS depression, hypotension, constipation, withdrawal, nausea and vomiting, hyperalgesia, and delirium. The associated clinical and financial implications of adverse events are significant because they carry the risk of prolonged duration of mechanical ventilation and increased ICU and hospital lengths of stay and an associated increase in costs (Devlin 2013).

Respiratory Depression and Oversedation

Opioid-associated respiratory depression is sometimes used clinically to aid in oxygenation by facilitating patient synchrony with mechanical ventilation. However, it can represent a barrier to successful liberation from mechanical ventilation, emphasizing the importance of careful dose titration and establishment of patient-specific goals.

The Joint Commission has identified risk factors for respiratory depression and oversedation, including age older than 60 years, opioid naivety, excessive opioid exposure, morbid obesity, sleep apnea, comorbidities including pulmonary or cardiac dysfunction, concurrent use of other sedating agents, conditions that impede diaphragmatic function (e.g., thoracic surgery), and a history of snoring or smoking. With few exceptions, these risk factors are not modifiable, but strategies to limit the adverse effect include the systematic evaluation of pain; the use of a multimodal approach, when feasible; and consideration of the use of enteral methadone to facilitate the discontinuance of continuous infusions of opioids. The Joint Commission website has a more comprehensive discussion.

Hypotension

Opioid-induced hypotension is typically associated with morphine and its ability to cause histamine release and venodilation. Blood pressure changes can occur with other opioids as well and are generally the result of blunting of the stress response and associated catecholamine release that are a physiologic response to painful stimuli.

Opioid-Induced Constipation

An estimated 40%–90% of patients will experience opioid-induced constipation, which often gives rise to discomfort, agitation, and a delay in meeting nutritional goals. The opioids stimulate GI μ-opioid receptors, which leads to an inhibition of gastric emptying, increased non-propulsive contractions, delays in GI transit in both the small and large intestines, and reduction in water and electrolyte secretion (Chey 2014). Constipation has been associated with adverse clinical outcomes, including inadequate oxygenation, hypotension, longer ICU stays, and even mortality (Gacouin 2010). Although supportive data suggesting benefits in clinical outcomes are sparse, efforts to promote defecation with stool softeners and laxatives should be considered for almost all opioid-treated patients. If opioid-induced constipation is refractory to standard interventions, the peripherally active μ-opioid antagonists methylnaltrexone and naloxegol can be used because they do not cross the blood-brain barrier to interfere with the opioid-mediated analgesic activity. Methylnaltrexone is administered subcutaneously, and the weight-based dose should be adjusted in renal disease. Naloxegol, which is enterally administered, requires dose adjustment when concurrently administered with CYP3A4 inhibitors. Both agents are contraindicated in patients with GI obstruction because of the risk of perforation.

Withdrawal

Few data describe the risk factors, characteristics, and management of opioid withdrawal in adult ICU patients. The most commonly described symptoms are nonspecific (e.g., agitation, diarrhea, vomiting, tachycardia, tachypnea) and mandate heightened caregiver awareness. The incidence of opioid withdrawal is not well defined but may approach 30% in mechanically ventilated patients receiving high-dose opioids for a week or more (Cammarano 1998). The PAD guidelines recommend tapering these drugs over several days, if possible, to avoid withdrawal symptoms (Barr 2013).

Nausea and Vomiting

Opioid-induced nausea and vomiting may be related to direct stimulation of chemoreceptor trigger zone. Treatment options are similar to those for postoperative patients.

Hyperalgesia

Opioid-induced hyperalgesia (OIH), identified more than 100 years ago, leads to increased pain response to minimal noxious stimuli (allodynia) or even the sensation of pain without noxious stimuli after exposure to this class of analgesics. The acute impact of OIH involves unrelieved pain, but the loss of analgesia because of OIH may lead to chronic pain in almost half of ICU survivors 6 months to 1 year after ICU discharge (Reardon 2015). A proposed mechanism for OIH involves sensitization of the pro-nociceptive pathways for pain by activation of NMDA receptors. This causes an influx

of intracellular calcium and heightens pain response. This mechanistic explanation provides a rationale for using NMDA antagonists such as ketamine and methadone for patients in whom OIH may be present (Chu 2008). Data also suggest a role of prostaglandins in the development of OIH by increasing the release of glutamate in the spinal cord dorsal horn that activates NMDA receptors.

A recent systematic review and meta-analysis of 27 randomized controlled trials involving 1494 patients evaluated the clinical impact of high-dose intraoperative opioid use and subsequent perception of pain post-surgery (Fletcher 2014). Remifentanil use increased pain intensity 24 hours after surgery and resulted in an increase in 18 mg of morphine administered during that observation period. Of interest, there was no difference in morphine-associated adverse drug events, despite the increased dose.

Currently, reasonable approaches to OIH include careful opioid dose titration and opioid rotation with methadone, as well as the use of multimodal analgesic strategies with agents such as the NSAIDs, ketamine, and α_2-agonists or the use of regional anesthetic techniques (Belgrade 2010).

Delirium

Cohort trials have inconsistently identified opioid use as a risk factor for developing delirium, but this relationship is confounded by the presence of pain (presumably the reason for using the opioid), which of itself can lead to delirium. One high-quality double-blind randomized trial compared dexmedetomidine with morphine in cardiac surgery patients; no between-group differences were found in the incidence of delirium, but the duration of delirium was longer in patients receiving morphine (Shehabi 2009).

SPECIAL POPULATIONS AND ISSUES

Neurologic and Other Patient Populations

The approach to pain management in the neurocritically ill population includes identifying potential causes of pain/discomfort, providing a close observation of all the variants of patient behaviors related to pain, and administering an analgesic trial when uncertainty about pain is present. A comprehensive online review describes pain assessment for nonverbal patients and updated tools, guidelines, and forms to facilitate bedside application.

A study of 439 assessments in 151 neurologic ICU patients showed that self-report of pain is feasible in almost 70% of patients with brain injury (Yu 2013). These data suggest that a self-report pain assessment strategy should be tried first and in a serial fashion because the ability to self-report waxes and wanes. When self-report is impossible, behavioral pain scales can be considered as long as motor function is intact. It should be appreciated, however, that behavioral responses to pain differ between patients with brain injury and other ICU patients, especially if they have an altered level of consciousness (Gelinas 2013). These patients may respond to noxious stimuli with sudden eye opening, weeping, and limb flexion, whereas typical behaviors such as grimacing and muscle rigidity occur less commonly. Similar to other patient populations, changes in most vital signs have not consistently correlated with painful stimuli, but changes in respiratory rate correlate with pain in traumatic brain injury; however, such changes occur only in patients who are conscious, as measured by a Glasgow Coma Scale score of 13 or more (Arbour 2014).

Brain activity studies of patients with brain injury who are in a vegetative or minimally conscious state support the concept that these patients may have the ability to perceive pain (Gelinas 2013). Pain assessment and management may be particularly important in this group of patients because pain is associated with an increased ICP, a reduction in cerebral venous outflow, and increasing brain metabolism. Furthermore, behavioral signs may be muted because these patients are often deeply sedated to prevent dangerous ICP elevations.

In the critically ill population with brain injury and an altered level of consciousness, pain assessment has yet to be rigorously developed; however, all patients should be evaluated and treated using an analgesic agent with a short half-life that will facilitate frequent neurologic examinations. Adequate analgesia is mandatory for patients with elevated ICP, with special attention during painful procedures. Data suggest that opioid use is related to transient increases in ICP that are likely related to reductions in systemic blood pressures and the resultant autoregulatory cerebral vasodilatation that follows (Roberts 2011). The clinical significance of these findings is uncertain. No firm guidance on the choice of agents exists, but fentanyl and remifentanil may be preferred because they seem to minimally alter cerebral perfusion and minimally interfere with hemodynamic stability.

Dementia

Patients with severe cognitive impairment may be unable to understand and even answer simple questions about their pain, making self-report a less valuable assessment tool. In addition, typical pain-related behaviors are often absent; therefore, caregivers need to be aware of other findings associated with pain in this population such as agitation, confusion, or combativeness. The most common causes of pain in patients with dementia have their origins in musculoskeletal disorders, neuropathies, and acute issues such as falls and infections.

Delirium

Until recently, the ability to evaluate pain in patients with delirium was unknown because this group of patients was excluded from validation studies. Validity of the CPOT was confirmed in a select group of patients with delirium without cognitive impairment and a median Richmond Agitation-Sedation Scale score of zero by comparing measurements before and after painful and nonpainful stimuli. The mean difference between CPOT scores at baseline and after painful procedures was 3

points on an 8-point scale. No such difference was seen with nonpainful procedures (Kanji 2016).

Subarachnoid Hemorrhage–Related Headache

Headaches in patients with subarachnoid hemorrhage occur with a prevalence of 75% during hospitalization; these can be severe and persist for as long as 2–9 years. Data suggest that headache is a leading cause of 30-day hospital readmission for these patients. There are no evidence-based guidelines for managing headaches in this population, though several agents have been used, including NSAIDs, opioids, acetaminophen, gabapentin, dexamethasone, and the combination product containing butalbital, acetaminophen, and caffeine (Glisic 2016).

Pharmacologic Paralysis

Therapeutic paralysis is infrequently used in most ICU patients, except in the setting of acute respiratory distress syndrome and for shivering during targeted temperature management. By definition, these patients cannot self-report and do not have motor activity to guide pain assessment. It is reasonable to assume that significant pain is present and to offer analgosedation as a baseline strategy to ensure comfort (May 2015).

Kidney Disease

Many opioids, including oxycodone, codeine, dihydrocodeine, meperidine, and morphine, degrade to active metabolites and should be used with caution, if at all, in patients with renal disease. Morphine is metabolized to morphine-3-glucuronide (55%) and morphine-6-glucuronide (10%), both of which are renally cleared. Morphine-6-glucuronide has a greater affinity for the μ-opioid receptor than morphine and has prolonged activity because of its slow egress from the CNS and its marked increase in half-life with renal impairment (from 2 to 27 hours in end-stage renal disease). Morphine-3-glucuronide has no analgesic activity, but it is reported in animal studies to be neurotoxic.

Hydromorphone is generally thought to be safe in the setting of renal disease, but recent data suggest that the metabolite, hydromorphone-3-glucuronide, is neurotoxic and may accumulate with impaired glomerular filtration (Gagnon 2015).

As previously mentioned, ICU data do not support the widely held notion that the clearance of fentanyl (an opioid without active metabolites) is significantly affected by kidney function.

Methadone is metabolized to inactive products, and only 20% of the parent drug is eliminated unchanged; it requires no dose adjustment for kidney disease.

Tramadol and its active metabolite, *O*-desmethyltramadol, can accumulate in renal disease. Prolongation of the dosing interval is recommended for patients with a GFR less than 30 mL/minute/1.73 m^2 and avoidance of the extended-release formulation.

Buprenorphine is degraded to metabolites with little analgesic activity. These metabolites accumulate in the setting of renal disease, but associated adverse reactions have not been characterized.

The United Kingdom Medicines Information Pharmacists Group website has a comprehensive document on the safe use of opioids in the setting of renal impairment.

Palliative Care

The incidence of moderate to severe pain in the final 3 days of life in hospitalized patients is about 40% and represents the greatest fear for this population. A recent review offers a stepwise approach to pain in the setting of palliative care, beginning with acetaminophen or an NSAID and advancing to use of an opioid for treating moderate to severe pain. Frequent bolus doses of opioids should be administered until pain is relieved, and these doses can help determine the approximate daily dose of opioid that can be administered as a basal dose using an infusion or scheduled intermittent administration. Provision of intermittent bolus medication for breakthrough pain should also be offered. Patients with neuropathic pain will require a different approach, as mentioned previously, with the use of the combination of an opioid with gabapentin. Other agents that may have utility include glucocorticoids, transdermal lidocaine, antidepressants, and anticonvulsants (Blinderman 2015).

Transitions of Care

A large proportion of ICU patients will receive pain medications during their acute illness; these may be discontinued when pain is no longer an issue, but some patients will require continuation of their analgesia. Consideration for using fentanyl patches, methadone, and oral opioids typically within a multimodal approach with nonopioid analgesics can help facilitate the discontinuance of intravenous infusions of opioids, allow for the transfer of patients to non-ICU settings, and avoid opioid withdrawal symptoms.

The risk specific to the inadvertent continuation of analgesics has yet to be described in the literature, but data analyses of other types of drugs consistently show that 20%–30% of patients continue to receive therapeutic agents begun in the ICU and even after discharge from the hospital, even though they are no longer indicated (Buckley 2015; Kram 2015). Pharmacists can play an important role in limiting this occurrence by medication reconciliation efforts as patients transition from the ICU to another nursing unit, health care setting, or home.

OUTCOMES MEASURES AND QUALITY IMPROVEMENT METRICS

The Joint Commission offers a comprehensive systems approach to improving pain management. It includes guidance on identifying the gaps and opportunities for improving pain management together with specific components of a successful pain management program. The central aspects of any process improvement effort include the prompt recognition and treatment of pain, the involvement of patients

and families in the pain management plan, and the tracking of improved treatment patterns, as well as reassessing and adjusting plans as needed.

Patient Satisfaction

There are financial incentives for improving patient satisfaction from effective pain management. The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) initiative by the Centers for Medicare & Medicaid Services (CMS) surveys patients after hospital discharge about pain management. In the future, these survey results may dictate payment from CMS and appear in public forums.

Acute Pain

More than 75% of patients remember pain and say that it was the most traumatic memory of their ICU experience. The PAD guidelines suggest that ICUs monitor the percentage of time that pain is assessed, with a goal of at least four times per nursing shift. Furthermore, an intervention to relieve pain should be documented within 30 minutes of identifying pain, together with documentation of its effectiveness. Preprocedural analgesia or nonpharmacologic interventions should also be recorded and tracked (Barr 2013).

Chronic Pain

Pain that exceeds the average duration beyond 2–3 months and has no apparent protective function is defined as chronic pain (Battle 2013). A recent survey suggests that 44% of patients experience pain 6 months to 1 year after ICU discharge, and the most common complaint involves shoulder pain. Risk factors for chronic pain include age, duration and severity of pain, and severe sepsis during critical illness.

Treatment of chronic pain is strongly debated in this era of widespread opioid abuse. There are no high-quality data on the long-term use of opioids for chronic pain, and there is no standardized therapeutic approach. As with any chronic disease, an individualized tactic with careful consideration of the risks and benefits of therapy is needed. The FDA has encouraged comprehensive training of prescribers about this incredibly complex issue (Alford 2016).

Posttraumatic Stress Disorder

Triggers for ICU-related PTSD are thought to be largely related to delusional memories, but several studies have implicated factual memories including trauma, injuries, and pain as important contributors. Recent data suggest that opioid exposure is associated with post-ICU psychiatric symptoms, including depression, anxiety, and PTSD (Huang 2016; Griffiths 2007). The observational cohort design of these studies does not allow for discrimination of opioids as causal factors or surrogates for pain in the development of PTSD. Supporting the latter contention are data from patients injured during combat, in whom the use of morphine reduced the risk of PTSD (Holbrook 2010).

FACILITATING BEDSIDE APPLICATION

The American Society for Pain Management and the American Association of Critical-Care Nurses have suggested a hierarchy of pain assessment techniques that begin with using patient self-report; identifying potential causes of pain such as procedures or pathologic conditions; using behavioral pain assessment tools; acknowledging the lack of specificity of vital signs for pain assessment; using surrogate reporting such as information obtained from family, friends, or caregivers; and finally, if there is reason to suspect pain, offering an analgesic trial, which can be diagnostic as well as therapeutic (Kerr 2006). Supportive information on this strategy for pain management is available online.

Data consistently suggest that a multifaceted approach to changing bedside practice offers the most effective and sustained strategy to improve pain management. Pain management protocols promise to limit practice variation by facilitating best practice to the bedside, providing timely response to pain, and allowing clear communication of treatment goals. Essential components of any pain management protocol include pain assessment tools and their frequency of application, together with desired goals of therapy and therapeutic options that are based on patient context. Order sets based on institution-specific protocols should be created to offer real-time clinical decision support and facilitate practice changes. Daily rounding with a pharmacist or using a quality checklist with the elements of a protocol should be considered as a way to support these efforts by verifying that pain has been addressed in a systematic fashion.

For patients with complex issues and unresolved pain, including referral sources such as an anesthesia-based pain consult service should be considered. These specialists have a wide array of available options for pain relief and can offer local or regional interventions.

CONCLUSION

Most ICU patients experience significant pain and regard it as the most traumatic memory of their illness. Achievement of adequate analgesia is often suboptimal for many reasons, including the inability to easily assess pain for many patients, lack of appreciation for the pain endured at rest and during routine procedures, and lack of a systematic approach for treatment. Data consistently show gaps in clinical performance that include a limited use of behavioral pain assessment tools in ICUs, inappropriate use of vital signs as indicators of pain, and inadequate documentation of pain and titration to identified targets. Some of these issues can be mitigated by providing light sedation that allows for patient self-report and participation in the treatment plan, but most can be rectified by simply offering a systematic protocolized approach with real-time reminders in an electronically based medical record.

There are many frontiers to explore regarding pain management. The most prominent involves the critically ill patient with significant neurologic disease. The pharmacist must be able to better characterize, identify, and manage this pain effectively, as well as overcome the barriers to better pain management that involve caregivers and health care systems. Caregivers must recognize that their understanding about the presence and severity of pain is often incorrect and that using validated pain assessment tools can improve clinical outcomes. Health care systems must foster an environment that focuses on relief from pain and provides adequate resources in personnel and clinical decision support to ensure that pain relief occurs.

Practice Points

Clinical management of ICU pain is evolving as our understanding of its etiology, risk factors, and consequences advances. Unfortunately unrelieved pain remains a common clinical issue and requires continual health care provider vigilance and attention to the following in order to make the ICU a more humane environment:

- **Systematic evaluation of pain at least four times during a nursing shift with valid assessment tools such as NRS and CPOT**
- **Identification of sources of pain (including routine ICU procedures) along with remedial strategies**
- **Appreciation of acute and long-term outcomes associated with unrelieved pain including chronic pain and hyperalgesia**
- **Consideration of potentially useful nonpharmacologic approaches to pain management (music, deep breathing, ice therapy)**
- **Provision of pharmacologic strategies that are based on patient context including the type and severity of pain, hemodynamic stability, prior response or tolerance to therapy, organ dysfunction, drug interactions, and QTc prolongation**
- **Consideration of an analgesia first (analgosedation) approach for ICU agitation because pain and discomfort are the most common precipitants**
- **Implementation of a multimodal approach to pain relief to augment analgesia and to limit adverse events in selected patients**
- **Anticipation and mitigation of adverse drug events such as interference with respiratory drive and gastrointestinal function, hypotension, withdrawal, and hyperalgesia**
- **Implementation of standards of practice through multifaceted approaches to ensure optimal patient-specific pain management is in place**

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Self-Assessment Questions

1. Three months ago, a 26-year-old man (height 71 inches, weight 92 kg) was admitted to the ICU with new-onset tetraparesis in the setting of a recent upper respiratory tract infection. He was given a diagnosis of Guillain-Barré syndrome and completed immunotherapy with intravenous immunoglobulin (0.4 g/kg for 5 days). Now, he is experiencing significant paraesthesias and dysesthesias in his legs during physical therapy while recovering in the ventilator step-down unit. Which one of the following best describes the inhibition or facilitation of pain input from the brain in this patient?

   A. Perception
   B. Modulation
   C. Transduction
   D. Excitation

2. A 45-year-old man (height 71 inches, weight 90 kg) is being treated in the medical ICU for acute respiratory failure caused by a left-sided parapneumonic effusion. On presentation, an indwelling pleural catheter was placed, and pleural fluid was sent for culture, which subsequently grew *Streptococcus pneumoniae*. The patient has been mechanically ventilated and treated with ceftriaxone 2 g intravenously daily and is clinically improving. On ICU day 7, the respiratory therapist completes endotracheal tube suctioning for increased secretions. That same day, the nurse obtains a basic metabolic panel from peripheral blood after inserting a new peripheral intravenous line. Later, on ICU day 7, the team decides to remove the indwelling pleural catheter after a series of reassuring chest radiographs and minimal drainage. Which one of the following ICU day 7 procedures was likely the most painful for this patient?

   A. Endotracheal tube suctioning
   B. Peripheral intravenous line insertion
   C. Peripheral blood obtainment
   D. Chest tube removal

3. A 77-year-old man (height 69 inches, weight 85 kg) is being treated in the ICU for acute respiratory distress syndrome caused by *Pseudomonas aeruginosa* community-acquired pneumonia. He is on hospital day 2 and is being mechanically ventilated. His vital signs include heart rate 102 beats/minute, blood pressure 165/98 mm Hg, temperature 98.8°F (37.1°C), and respiratory rate 17 breaths/minute. His current drugs include piperacillin/tazobactam 3.375 g intravenously every 8 hours, fentanyl 50 mcg/hour, propofol 40 mcg/kg/minute, norepinephrine 0.1 mcg/kg/minute, cisatracurium 37.5 mg/hour, heparin 5000 units subcutaneously every 12 hours, docusate 100 mg twice daily, and sucralfate 1 g every 6 hours. On multidisciplinary rounds, the nurse states she is going to turn off the fentanyl infusion because the patient's most recent CPOT score was zero. Which one of the following is best to recommend for this patient?

   A. The fentanyl infusion can be turned off because the CPOT score is 0, which is below the threshold of 2 for pain identification.
   B. The nurse should be monitoring the patient's vital signs for tachycardia and hypertension, which are proven indicators of pain in the ICU.
   C. CPOT scores cannot be used in this patient because he is being paralyzed with cisatracurium.
   D. A surrogate should be asked to assess the patient's pain before fentanyl is titrated.

4. Which one of the following patient profiles most accurately describes the possible long-term negative impact of unrelieved pain in the ICU?

   A. 62-year-old woman who is experiencing chronic shoulder pain and reduced quality of life, as evidenced by less autonomy and an inability to complete her activities of daily living.
   B. 59-year-old woman with new-onset major depressive disorder and generalized anxiety disorder.
   C. 60-year-old man with cognitive impairment, as evidenced by low scores on the Repeatable Battery for the Assessment of Neuropsychological Status and immobility requiring him to remain in bed most of the time.
   D. 64-year-old man with new-onset dementia and economic hardship because of medical expenses.

5. Staff at your ICU are implementing the recommendations for pain assessment, treatment, and prevention from the 2013 PAD guidelines care bundle. They are specifically interested in increasing pain assessments. As the pharmacist on staff, you highlight the importance of routine pain assessments. Which one of the following is most likely to result from routine pain assessments?

   A. Increase in patient discharge to home after hospitalization.
   B. Decrease duration of mechanical ventilation.
   C. Decrease in the incidence of ICU delirium.
   D. Decrease in the need for tracheostomy.

6. A 72-year-old woman (height 65 inches, weight 70 kg) presents after coiling of a left anterior cerebral artery aneurysm that ruptured. She is post-bleed day 5. The patient has remained intubated because of her inability to protect her airway. Her current drugs include dexmedetomidine 0.7 mcg/kg/hour, fentanyl 50 mcg hourly as

needed for pain, heparin 5000 units subcutaneously every 12 hours, sucralfate 1 g every 6 hours, aspirin 81 mg daily, atorvastatin 40 mg daily, nimodipine 60 mg every 4 hours, and fludrocortisone 100 mcg twice daily. The nurse is preparing to turn the patient and would like a recommendation for procedural pain management. Which one of the following is best to recommend for this patient?

A. 300 mg of gabapentin once before turning
B. 2 mg of enteral hydromorphone once before turning
C. 100 mcg of intravenous fentanyl once before turning
D. 100 mcg of intravenous fentanyl once after turning

Questions 7–9 pertain to the following case.

P.S. is a 62-year-old man (height 72 inches, weight 95 kg) with a history of depression, seizures, and coronary artery disease. He is being treated for methicillin-sensitive *Staphylococcus aureus* bacteremia of unclear etiology. P.S. is currently in septic shock and is intubated and sedated in the medical ICU. His pertinent laboratory results are as follows: Na 140 mEq/L, K 4.8 mEq/L, Cl 100 mEq/L, glucose 143 mg/dL, and SCr 3.2 mg/dL (baseline 0.9 mg/dL). P.S.'s urine output has been 0.2 mL/kg/hour. His current drugs include propofol 30 mcg/kg/minute, fentanyl 75 mcg/hour, norepinephrine 0.3 mcg/kg/minute, hydrocortisone 50 mg intravenously every 6 hours, heparin 5000 units subcutaneously every 12 hours, sucralfate 1 g every 6 hours, simvastatin 40 mg daily, aspirin 81 mg daily, levetiracetam 500 mg every 12 hours, and fluoxetine 80 mg daily. P.S.'s Sedation-Agitation Scale (SAS) score is 3 (sedated, but responds to simple commands), and his CPOT score is 2.

7. The medical intern is seeking pain management advice for P.S. but is concerned about fentanyl accumulation in the setting of acute kidney injury. Which one of the following is best to recommend for P.S.?

   A. Switch to hydromorphone 2-mg intravenous bolus; then initiate an infusion at 1 mg/hour to avoid fentanyl accumulation in renal failure.
   B. Discontinue the fentanyl infusion, and initiate fentanyl 100 mcg every hour as needed for pain to avoid accumulation in the setting of renal failure.
   C. The patient needs no analgesia because his most recent CPOT score was 2.
   D. Continue the current infusion fentanyl infusion rate because the patient's pain is well controlled, and fentanyl does not accumulate to a clinically significant degree in the setting of renal failure.

8. Five days later, the nurse approaches you about P.S.'s pain management. He has been scoring 6 or 7 on the CPOT, and there is concern that he is experiencing pain, despite receiving 200 mcg/hour of fentanyl. P.S.'s laboratory test results at this time are as follows: Na 141 mEq/L, K 4.9 mEq/L, Cl 101 mEq/L, glucose 160 mg/dL, and SCr 3.7 mg/dL (baseline 0.9 mg/dL). His urine output has been about 0.1 mL/kg/hour. Which one of the following is best to recommend to manage P.S.'s pain?

   A. Double the fentanyl dose to 400 mcg/hour.
   B. Discontinue the fentanyl infusion and bolus with 1 mg of hydromorphone, and if the patient responds, initiate a hydromorphone infusion at 1.5 mg/hour.
   C. Discontinue the fentanyl infusion and bolus with 10 mg of morphine, and if the patient responds, initiate a morphine infusion at 7.5 mg/hour.
   D. Continue the current fentanyl infusion rate, and add adjunctive tramadol 100 mg every 6 hours as needed.

9. Ten days into P.S.'s hospitalization, the nurse notifies the team that he has not had a bowel movement. He had been tolerating enteral tube feeds at 40 mL/hour, but now, he has significant gastric residuals of greater than 500 mL. P.S.'s laboratory results at this time are as follows: Na 139 mEq/L, K 5.0 mEq/L, Cl 98 mEq/L, glucose 158 mg/dL, and SCr 3.9 mg/dL (baseline 0.9 mg/dL). His urine output is 0.2 mL/kg/hour. A kidney, ureter, and bladder radiography reveals no obstruction, and the patient has a nasogastric tube in place. The team would like to administer a drug for suspected opioid-induced constipation. P.S. has not responded to docusate 100 mg every 12 hours, bisacodyl 10 mg rectally daily, and polyethylene glycol 17 g daily. Which one of the following is best to recommend for P.S.?

   A. Methylnaltrexone 12 mg subcutaneously every 48 hours as needed
   B. Naloxone 1 mg three times daily by nasogastric tube until a bowel movement occurs
   C. Methylnaltrexone 6 mg subcutaneously every 48 hours as needed
   D. Naloxegol 12.5 mg once daily by nasogastric tube until a bowel movement occurs

10. A 40-year-old man (height 71 inches, weight 101 kg) with a history of intravenous drug abuse (opioids) is admitted to the surgical ICU with septic shock caused by necrotizing fasciitis of his left lower extremity. Three days into his ICU stay, he continues to report substantial pain because of serial debridement (NRS-V score 10/10). His current drugs include hydromorphone 6 mg intravenously every 4 hours, fentanyl 200 mcg intravenously every hour as needed for moderate to severe pain (2000 mcg in the past 24 hours), heparin 5000 units subcutaneously every 8 hours, docusate 100 mg every 12 hours, polyethylene glycol powder 17 g by mouth daily, vancomycin 1500 mg every 12 hours, piperacillin/tazobactam 4.5 g intravenously every 8 hours, and clindamycin 900 mg intravenously every 8 hours. The care team decides to consult the acute pain management service, which recommends initiating a ketamine infusion. Which one of the following properties of this agent is the most likely reason for this recommendation?

A. It is a GABA receptor antagonist, which may restore analgesia.
B. It is a NMDA receptor antagonist, which may restore analgesia.
C. It is a sigma opioid receptor agonist, which may increase the pain threshold.
D. There is no clear indication for ketamine in this patient, and the recommendation should be rejected.

11. A surgical resident is preparing to take a patient to the operating room for an exploratory laparotomy because of concern for an ischemic bowel. The resident is interested in administering perioperative lidocaine to reduce the need for opioids postoperatively and to expedite the return of bowel function. Which one of the following is best to recommend for this patient?

A. Give 1 mcg/kg intravenous loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
B. Give 1 mg/kg intramuscular loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
C. Give 1 mg/kg intravenous loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
D. No data support using lidocaine for this indication.

12. A 52-year-old man is being treated for a right middle cerebral artery ischemic stroke in the neurologic ICU. He has received tissue plasminogen activator and endovascular clot extraction, but he is at a high risk of malignant cerebral edema because he has infarcted more than two-thirds of his right middle cerebral artery territory. The patient is currently intubated and sedated because of an aspiration pneumonia. The neurosurgeon would like to provide analgosedation with remifentanil so that frequent neurologic examinations can reliably be done. The neurologic ICU team is unfamiliar with this agent, and they ask you why the neurosurgeon has ordered it. Which one of the following is the most appropriate response to this question about remifentanil?

A. It is rapidly metabolized by CYP3A4 to inactive metabolites, leading to a short and predictable half-life.
B. It is inexpensive and can be substituted for fentanyl purely on the basis of cost savings.
C. It is rapidly metabolized by nonspecific tissue and plasma esterases to inactive metabolites, leading to a short and predictable half-life.
D. It is rapidly metabolized by glucuronidation to its active metabolite, remifentanil acid, which is renally eliminated.

13. A 32-year-old man (height 72 inches, weight 100 kg) is being treated in the surgical ICU after a fall that resulted in several rib fractures and a pelvic fracture. He has undergone tracheostomy and percutaneous endoscopic gastrostomy and is ready to transition to the ventilator step-down unit. The team has been trying to wean the patient off a hydromorphone infusion for the past week without success. The intensivist would like to transition the patient to enteral methadone. The patient is not receiving QTc-prolonging agents and has normal liver function. If transitioned to methadone, which one of the following is this patient most likely to experience?

A. Shorter ICU length of stay
B. Reduced total duration of mechanical ventilation
C. Shorter hospital length of stay
D. Faster mechanical ventilator weaning

14. A 25-year-old woman (height 64 inches, weight 70 kg) is being treated for a traumatic brain injury in the surgical ICU after a motor vehicle crash. She has several small intraparenchymal hemorrhages and a diffuse subarachnoid hemorrhage. An external ventricular device was placed for early hydrocephalus. The patient's intracranial pressure has been 30–35 mm Hg, despite hyperventilation, permissive hypernatremia, and mannitol boluses. A pentobarbital infusion has been initiated for refractory intracranial pressure. The pulmonary/critical care fellow would like a recommendation on how to manage her analgosedation. Which one of the following is best to recommend for this patient?

A. Morphine 5–10 mg intravenously every 2 hours as needed for pain.
B. Ketorolac 15 mg intravenously every 6 hours for 5 days.
C. Hydromorphone 2-mg bolus; then 1–5 mg/hour as a continuous infusion.
D. Fentanyl 100-mcg bolus; then 25–100 mcg/hour as a continuous infusion.

15. A 63-year-old woman (height 64 inches, weight 68 kg) is being treated in the medical ICU for a UTI caused by an extended-spectrum β-lactamase–producing *Escherichia coli*. Her current drugs include fentanyl 50 mcg intravenously every 1 hour as needed for pain, midodrine 10 mg every 8 hours, meropenem 1 g intravenously every 8 hours, heparin 5000 units subcutaneously twice daily, aspirin 81 mg daily, lovastatin 20 mg daily, and citalopram 20 mg daily. The patient's confusion assessment method for the ICU assessment is positive, and her answers to questions about pain are nonsensical. The medical resident would like to use another pain assessment method.

Which one of the following is best to recommend for this patient?

A. Use the BPS.
B. Use the CPOT.
C. Monitor for tachycardia and hypertension.
D. Use the pain-behavioral assessment tool.

16. A 37-year-old woman (height 66 inches, weight 77 kg) is recovering from a subarachnoid hemorrhage caused by a ruptured posterior communicating artery aneurysm. She underwent coil embolization and is now post-bleed day 22. The patient is experiencing severe headaches, and the neurocritical care team is looking for help with her pain management. Her current drugs include ibuprofen 600 mg every 6 hours, butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg 2 tablets every 4 hours, dexamethasone 2 mg every 6 hours, oxycodone 5–10 mg every 4 hours as needed for headache (one dose in the past 24 hours because of lack of response), fludrocortisone 200 mcg twice daily, and heparin 5000 units subcutaneously every 12 hours. Which one of the following is best to recommend for this patient?

A. Fentanyl 25 mcg/hr patch every 72 hours
B. Acetaminophen 975 mg orally every 6 hours
C. Gabapentin 300 mg orally every 8 hours
D. Methadone 5 mg orally every 8 hours

17. A 94-year-old woman in your medical ICU is being transitioned to comfort care in the setting of ovarian cancer. Her current laboratory values are as follows: Na 140 mEq/L, K 3.9 mEq/L, Cl 99 mEq/L, glucose 133 mg/dL, and SCr 1.1 mg/dL (baseline 0.9 mg/dL). She has been making more than 0.9 mL/kg/hour of urine over the past 24 hours. Her cognition remains intact, but she cannot swallow medications. The medical resident enters the following drugs for comfort care: ondansetron 4 mg intravenously every 8 hours as needed for nausea, lorazepam 1 mg intravenously every 3 hours as needed for anxiety, morphine 5 mg intravenously every 3 hours as needed for pain, acetaminophen 1000 mg intravenously every 6 hours as needed for pain, hydromorphone 2 mg intravenously every 4 hours as needed for pain, and glycopyrrolate 0.2 mg intravenously every 2 hours as needed for excessive secretions. Her SAS score is 3 (sleepy but able to respond to commands with stimulation), and her NRS-V score is 2, indicating mild pain. Which one of the following is best to recommend for this patient?

A. Hydromorphone 2 mg intravenously
B. Morphine 5 mg intravenously
C. Acetaminophen 1000 mg intravenously
D. No pain medications indicated in this setting

18. As the ICU pharmacist, you are asked to do a quality assurance project on the continuation of opioids and other psychoactive medications on ICU discharge. You unexpectedly find that 25% of patients are being discharged from the ICU on opioids. Which one of the following would best reduce the inappropriate continuation of these medications on ICU discharge?

A. Discontinue all opioids and psychoactive medications on ICU discharge.
B. Incorporate 5-day stop dates on all opioids and psychoactive medication orders for ICU patients.
C. Continuing opioids and psychoactive medications in 25% of patients is acceptable and does not require remediation.
D. Do medication reconciliations on transitions of care to ensure that opioids and psychoactive medications are appropriately continued or discontinued.

Questions 19 and 20 pertain to the following case.

The ICU staff at HealthSure Hospital is seeking to improve their pain management practices. As the staff pharmacist, you review the 2013 PAD guidelines and make several clinical improvements, but you would like to make some systems changes as well (e.g., tracking improvement, workflow optimization).

19. Which one of the following organizations would be the best resource in forming the HealthSure Hospital systems approach to improving pain management?

A. Joint Commission
B. Agency for Healthcare Research and Quality
C. Pharmacy Practice Model Initiative
D. Centers for Medicare & Medicaid Services

20. Which one of the following organizations would be best for the HealthSure Hospital team to consult for a hierarchy of pain assessment techniques?

A. American College of Clinical Pharmacy
B. American Society of Health-System Pharmacists
C. American College of Critical Care Medicine
D. American Association of Critical-Care Nurses

Learner Chapter Evaluation: Pain and Analgesia.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Apply knowledge of the incidence, etiologies, and assessment of pain to the treatment of critically ill patients.
13. Develop evidence-based pain management strategies that include both nonpharmacologic and pharmacologic interventions and that account for transitions of care.
14. Design a pain control strategy for unique patient populations.
15. Evaluate short- and long-term outcomes associated with pain management, and develop methods to improve quality of care.
16. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Agitation in Mechanically Ventilated ICU Patients

By Joshua T. Swan, Pharm.D., MPH, BCPS

Reviewed by Stephanie Mallow Corbett, Pharm.D., FCCM; Jessica M. Louie, Pharm.D., BCCCP; and Nadia Ferguson-Myrthil, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Distinguish among the leading guidelines regarding drug therapy recommendations for prevention and treatment of agitation.
2. Measure patient level of sedation using valid and reliable screening tools that are recommended by clinical guidelines.
3. Evaluate appropriate goals for level of sedation on the basis of patient-specific characteristics.
4. Assess the differences in pharmacologic therapies for the treatment of agitation.
5. Develop a multidisciplinary sedation care plan that is coordinated with mechanical ventilation weaning activities to minimize the duration of mechanical ventilation.
6. Evaluate sedation-related factors that contribute to total ICU costs.

ABBREVIATIONS IN THIS CHAPTER

ABC	Awakening and Breathing Controlled (trial)
ABCDE	Awakening and Breathing Coordination, Delirium Monitoring and Management, and Early Mobility
PAD	Pain, agitation, and delirium
PRIS	Propofol-related infusion syndrome
RASS	Richmond Agitation-Sedation Scale
RSI	Rapid sequence intubation
SAS	Sedation-Agitation Scale
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine

Table of other common abbreviations.

INTRODUCTION

Agitation is an elevated state of arousal that can lead to restless or combative behavior. The many causes of agitation among ICU patients include pain, delirium, anxiety, hypoxemia, hypoglycemia, hypotension, noise, sleep deprivation, and withdrawal from chronic psychoactive medications (Barr 2013; Reade 2014). If the underlying cause of agitation cannot be alleviated, the cornerstone pharmacologic approach is to administer intravenous sedatives. This chapter discusses the development of pharmaceutical care plans to prevent and treat agitation in adult ICU patients to achieve a goal level of arousal/sedation while minimizing short- and long-term adverse drug events. The predominant focus is on the sedation of mechanically ventilated adult ICU patients, given that mechanical ventilation for respiratory failure occurs in 33% of ICU patients, and up to 70% of these patients receive sedatives (Arroliga 2005; Esteban 2002; Gill 2012; Rotondi 2002). Some information on bedside procedural sedation is provided. Conscious sedation and pediatric sedation are beyond the scope of this chapter and are not included.

CLINICAL PRACTICE GUIDELINES

The most authoritative and comprehensive guideline addressing agitation in adult ICU patients is the 2013 Society of Critical Care Medicine (SCCM) pain, agitation, and delirium (PAD) guideline, which states that agitation is inextricably linked to

pain and delirium (Table 2-1) (Barr 2013). The multidisciplinary guideline committee developed recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, ranking quality of evidence as high (A), medium (B), or low (C). The strength of recommendations was ranked as strong (1) or weak (2). Use of the GRADE method was a significant improvement to the previous 2002 version of the SCCM guidelines, where some recommendations were made in the absence of evidence from clinical studies (Jacobi 2002).

ETIOLOGIES OF AGITATION AMONG CRITICALLY ILL PATIENTS

The many causes of agitation among ICU patients include pain, anxiety, and delirium (Barr 2013; Reade 2014). Pain causes anxiety, insomnia, delirium, and agitation (Barr 2013). During their ICU stay, most critically ill patients will have pain, which can occur at rest or in response to procedures (e.g., endotracheal suctioning, device insertion) (Barr 2013; Chanques 2007). Underlying anxiety disorders, anxiety related to anticipation of a procedure, or anxiety related to unwanted outcomes can lead to agitation among ICU patients. Anticipatory anxiety can be addressed through nonpharmacologic measures such as patient education and reassurance. Patients with delirium may also have symptoms of agitation: 23%–55% have transient agitation, and 2%–14% have a purely agitated state (Peterson 2006; Swan 2014).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the sympathetic and parasympathetic nervous systems
- Drug knowledge of the opioid agents used to treat pain in the ICU

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
- Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med 2014;370:444-54.
- Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs 2012;72:1881-916.
- Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. Crit Care Med 2010;38(6 suppl):S231-243.
- ICU Delirium and Cognitive Impairment Study Group [homepage on the Internet].

MEASUREMENT OF AGITATION AND SEDATION

Level of arousal can be measured subjectively by physical evaluation or objectively by measuring electrical activity in the brain. The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are two subjective sedation scales recommended by the 2013 SCCM PAD guidelines for routine assessment of depth and quality of sedation in mechanically ventilated adult ICU patients (Table 2-2) (Barr 2013). On the sedated spectrum, the subjective scales differentiate patients who arouse in response to verbal stimuli (i.e., light sedation) from patients who arouse only in response to physical stimulation (usually called deep sedation or coma). Advantages of these subjective measurement tools include their use by many health care professions (predominantly nurses and physicians); also, they can be adopted by new clinicians with relative ease and minimal training, are quick to administer, and do not require costly technology. A primary disadvantage of subjective measurement tools is their inability to assess patients who cannot physically participate. For instance, paralysis from neuromuscular blocking agents interferes with subjective assessment; thus, in this case, objective rather than subjective measures are used. Objective tools monitor electrical activity in the brain using probes attached to the skin on the head. Examples of these tools include auditory evoked potentials, bispectral index, Narcotrend Index, patient state index, and state entropy (Barr 2013).

INDICATIONS FOR SEDATION

The duration and depth of sedation vary by indication. Determining the appropriate indication for sedation is crucial in developing a sedation care plan.

Procedures

Procedures can cause pain, anxiety, and agitation. These procedures include central bloodstream catheter insertion, wound care, patient positioning for nursing care, bedside endoscopy, and endotracheal aspiration. Many procedures last less than 1 hour, and a single dose of a sedation medication is usually sufficient. The goal of sedation is to prevent agitation and provide comfort while maintaining a light-moderate level of sedation; therefore, sedatives are titrated to maintain target sedation using frequent measurements of level of arousal with recommended subjective tools (e.g., SAS, RASS).

Table 2-1. Guideline Recommendations for Preventing and Treating Agitation in Adults

Therapeutic Area	2013 SCCM PAD Guideline Recommendations for Adult ICU Patients
Depth of sedation	• Sedation medications should be titrated to a light, as opposed to deep, level of sedation, unless clinically contraindicated (+1B)[a] • Light levels of sedationa: ◦ Improve clinical outcomes (B) ◦ Increase the physiologic stress response but do not increase the risk of myocardial ischemia (B) • It is unclear whether depth of sedation is associated with psychological stress (C)
Monitoring of sedation	• The most valid and reliable subjective assessment tools for measuring quality and depth of sedation: ◦ RASS (B) ◦ SAS (B) • Objective measures of brain function: ◦ Are not recommended as the primary method to monitor depth of sedation in non-comatose, non-paralyzed critically ill adult patients (-1B)[b] ◦ Are recommended as an adjunct to subjective sedation assessments in adult ICU patients who are receiving neuromuscular blocking agents (+2B)[b] • EEG is recommended to monitor non-convulsive seizure activity in patients with either known or suspected seizures, or to titrate electro-suppressive medication to achieve burst suppression in patients with elevated intracranial pressure (+1A)
Choice of sedative	• Analgesia-first sedation is recommended in mechanically ventilated patients (+2B) • Non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred to sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated patients (+2B)
Delivery of sedation	• Daily sedation interruption or targeting a light level of sedation is recommended for mechanically ventilated patients (+1B)

[a]Light level of sedation represents a patient who is arousable and able to purposefully follow simple commands.

[b]Objective measures of brain function include auditory evoked potentials, bispectral index, Narcotrend Index, patient state index, and state entropy.

EEG = electroencephalogram; RASS = Richmond Agitation-Sedation Scale; SAS = Sedation-Agitation Scale.

Information from: Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.

Some procedures may require a moderate level of sedation to ensure immobility during critical moments of the procedure (e.g., bloodstream catheter insertion). Procedures elicit pain; therefore, pharmacologic strategies for procedural sedation usually include a potent intravenous analgesic (e.g., opioid). It is the responsibility of the critical care pharmacist to work with the medical providers performing the procedure to develop a care plan for procedural sedation that is appropriate for the goal level of sedation and expected duration of the procedure.

Rapid Sequence Intubation

Rapid sequence intubation (RSI) aims to increase the success rate of emergency intubation by administering a sedative followed by a neuromuscular blocking agent. The RSI procedure "generally consists of seven steps: (1) preparation, (2) preoxygenation, (3) pretreatment, (4) paralysis and induction, (5) protection from positioning, (6) placement of the tube in the trachea, and (7) postintubation management" (Mace 2008). In step 4, an induction agent is provided as a single intravenous bolus. The most commonly used induction agents for RSI are etomidate, midazolam, fentanyl, and ketamine (Mace 2008). The sequence of medication delivery is of utmost importance. Sedation induction is administered before the paralytic to allow ample time to exert its effect, thereby preventing the inhumane situation in which a patient is fully aware but paralyzed and unable to communicate.

Mechanical Ventilation

Mechanical ventilation is indicated for airway compromise or respiratory failure that may present as hypoxemia, hypercarbia, or increased work of breathing. Mechanical ventilation requires securing an invasive airway by placing an endotracheal tube (oral or nasal) or tracheostomy. Goals

Table 2-2. Conversion Between Subjective Sedation Scales

Level of Arousal	Richmond Agitation-Sedation Scale[b]	Sedation-Agitation Scale[c]
Severe agitation	+4, Combative	7, Dangerous agitation
	+3, Very agitated	6, Very agitated
Mild to moderate agitation	+2, Agitated	5, Agitated
	+1, Restless[a]	
Alert and calm, awakens easily and follows verbal commands	0, Alert and calm[a]	4, Calm and cooperative[a]
Light sedation	-1, Drowsy[a]	
	-2, Light sedation[a]	3, Sedated[a]
Moderate sedation	-3, Moderate sedation	
Coma, no response to voice	-4, Deep sedation	2, Very sedated
	-5, Unable to rouse	1, Unable to rouse

[a]Light levels of sedation that are ideal targets for sedation of mechanically ventilated adult patients.

[b]Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983-91B; Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.

[c]Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325-9.

Information from: Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92; Khan BA, Guzman O, Campbell NL, et al. Comparison and agreement between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in evaluating patients' eligibility for delirium assessment in the ICU. Chest 2012;42:48-54.

of mechanical ventilation are to provide adequate oxygenation, carbon dioxide clearance, and management of work of breathing; these goals are accomplished by manipulating respiratory rate, volume, pressure, flow rate, and fraction of inspired oxygen (FIO_2; ranging from room air at 0.21 to pure oxygen at 1.00) (Maung 2016).

Mechanical ventilation is a primary source of pain, discomfort, and agitation among critically ill patients (Esteban 2002; Payen 2007; Rotondi 2002). Placement of an endotracheal tube results in severe pain and stressful experiences, including the inability to speak, anxiety, a choking feeling, and sleep interference (Rotondi 2002). Up to 33% of ICU patients require mechanical ventilation for an average of 6 days during their ICU stay, and up to 70% of these patients will receive sedation therapy (Arroliga 2005: Esteban 2002). Mechanical ventilation is responsible for most sedation therapy given in the ICU.

Sedation agents are indicated during mechanical ventilation to prevent agitation and improve comfort, rather than induce sedation. This is an important distinction because some mechanically ventilated patients can tolerate mechanical ventilation without sedation (Strom 2010). Sedation can create a therapeutic paradox, whereby sedative-induced respiratory depression renders the patient incapable of being liberated from mechanical ventilation. The goal of therapy for these patients is to provide comfort without prolonging mechanical ventilation through sedative-induced respiratory depression and cognitive impairment.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NIPPV) refers to either intermittent positive pressure ventilation or continuous positive airway pressure through the patient's mouth, nose, or both (Gregoretti 2015). Compared with conventional invasive ventilation, NIPPV is less likely to interfere with a patient's native upper airways and cause iatrogenic complications such as infection (Gregoretti 2015). Noninvasive positive pressure ventilation can be used as a treatment modality for hypoxia or hypercapnia before initiating conventional invasive ventilation or as a modality to wean a patient off conventional invasive ventilation. Concurrent hypoxemia and NIPPV can cause discomfort and anxiety, and some patients will refuse to continue NIPPV. Therefore, opiates or sedatives can be used to alleviate anxiety and improve compliance with NIPPV (Huang 2012).

The goal for patients receiving noninvasive ventilation is to prevent transitioning to an invasive airway by optimizing

oxygen values (Sao_2 and Pao_2/Fio_2 ratio), serum pH, respiratory rate, and patient comfort. In a trial of patients receiving noninvasive ventilation requiring sedation, those randomized to dexmedetomidine infusion were less likely to require endotracheal intubation than those receiving a midazolam infusion (21% vs. 45%, p=0.043) and had shorter ICU care (mean ICU days, 4.9 vs. 8.5, p=0.042) (Huang 2012). However, continuous sedation has been associated with hypercapnia in patients receiving NIPPV, and larger controlled trials are needed to clarify the safety and role of sedation for NIPPV (Matsumoto 2015).

DEFINING TREATMENT GOALS FOR LEVEL OF SEDATION

Light Levels of Sedation

Unless clinically contraindicated, the 2013 SCCM PAD guidelines recommend that sedatives be titrated to a light level of sedation for adult mechanically ventilated ICU patients (Barr 2013). A lighter level of sedation is associated with decreased duration of mechanical ventilation and ICU length of stay (Table 2-3). A light level of sedation can be accomplished by titrating sedatives to a RASS of -2 to +1 or a SAS of 3 or 4 with frequent sedation monitoring or by daily spontaneous awakening trials (SATs).

Potential risks associated with light levels of sedation are physiologic and psychological stress. A light level of sedation is associated with transient increases in urine and serum catecholamine concentrations, heart rate, blood pressure, and respiratory rate. However, a light level of sedation does not increase the risk of myocardial ischemia, even among patients at high risk of cardiac events (Hall 1997; Kress 2007; Plunkett 1997; Terao 2003). Light sedation did not increase the risk of psychological outcomes in two randomized trials (Table 2-4). The 2013 SCCM PAD guidelines conclude that the potential benefits of light sedation clearly outweigh the potential risks (Barr 2013).

Indications for Deep Level of Sedation

Generally, a deep level of sedation is warranted for patients with ongoing surgical issues, receiving neuromuscular blocking agents, hemodynamic instability associated with myocardial ischemia, or with ongoing brain injury sensitive to elevations in intracranial pressure (Roberts 2012). A deep level of sedation may be appropriate for patients with postoperative open incisions or plans for subsequent operations (to prevent self-harm from agitation). Deep sedation should be provided for all patients who are paralyzed with neuromuscular blocking agents throughout neuromuscular blockage.

EVALUATION OF EFFECTIVENESS

Randomized trials evaluating sedation effectiveness in mechanically ventilated adults have used many primary end points (Table 2-5). Any care plan involving a sedation regimen should first establish a goal level of sedation that includes an upper and lower boundary, together with drug-specific titration directions that can be enacted when the level of sedation falls outside the goal range. The proportion of time that a patient spends within this goal level of sedation is a good clinical marker of efficacy. Another marker of efficacy is duration of mechanical ventilation, which greatly

Table 2-3. Trial Data on Improved Outcomes with Light Sedation

Study	Deep Sedation (control arm)	Light Sedation (intervention arm)	Difference in MV Days[a]	Difference in ICU Days[a]
(Brook 1999)	Non–protocol-directed sedation	Protocol-directed sedation	-1.5 days, p=0.003	-1.8 days, p=0.13
(Kress 2000)	Usual care	Daily SATs	-2.4 days, p=0.004	-3.5 days, p=0.02
(Girard 2008)	SBTs daily plus usual care	Paired SATs with SBTs daily	-3.1 days, p=0.02	-3.8 days, p=0.01
(Treggiari 2009)	Heavily sedated	Cooperative and interactive	-1 day, p=0.03	-1.5 days, p=0.03

[a]Calculated as light sedation minus deep sedation, where a negative number represents a decrease in days for patients receiving light sedation.

MV = mechanical ventilation; SAT = spontaneous awakening trial; SBT = spontaneous breathing trial.

Information from: Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27:2609-15; Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7; Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34; and Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 2009;37:2527-34.

Table 2-4. Trial Data on Level of Sedation and Post-ICU Psychological Stress

Study	Deep Sedation (control arm)	Light Sedation (intervention arm)	Outcome Assessment	Psychological End Points (deep sedation vs. light sedation)
(Treggiari 2009)[a]	Heavily sedated	Cooperative and interactive	4 wk after enrollment	PTSD, 10% vs. 9%, p=0.83 Anxiety, 12% vs. 12%, p=0.94 Depression, 4% vs. 8%, p=0.43
(Kress 2003)	Usual care	Daily SATs	≥ 6 mo after hospital discharge	PTSD, 32% vs. 0%, p=0.06 Anxiety Chronic, 63% vs. 46%, p=0.56 Acute, 21% vs. 30%, p=0.68

[a]Individual questions revealed that patients randomized to deep sedation were more likely to have "trouble remembering important parts of the stressful experience" (p=0.01) and "repeated, disturbing memories of the stressful experience" (p=0.05).

PTSD = post-traumatic stress disorder.

Information from: Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 2009;37:2527-34; and Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med 2003;168:1457-61.

Table 2-5. Primary Efficacy End Points for Sedated Mechanically Ventilated Adults in the ICU

Landmark Randomized Trials	Primary Effectiveness End Point
Daily interruption of sedative infusions (Kress 2000)	Duration of mechanical ventilation and lengths of stay for hospital and ICU
MENDS trial (Pandharipande 2007)	Days alive and free of delirium or coma within 28 days of randomization
ABC trial (Girard 2008)	Days alive and free of mechanical ventilation within 28 days of randomization
SEDCOM trial (Riker 2009)	Percentage of time within RASS goal range of -2 to +1
MIDEX/PRODEX trial (Jakob 2012)	Proportion of time at target RASS goal range of -3 to 0 without use of rescue sedation[a]
SLEAP trial (Mehta 2012)	Duration of mechanical ventilation

[a]First-line rescue sedation was midazolam (MIDEX trial) or propofol (PRODEX trial).

RASS = Richmond Agitation-Sedation Scale

Information from: Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7; Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53; Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34; Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60; and Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92.

affects patients (e.g., quality of life, immobility, discomfort) and health care systems (e.g., resource burden, high cost). A paradigm shift during the past decade has been recognition of the impact of sedation-induced respiratory depression on the inability to wean a patient from mechanical ventilation. In collaboration with respiratory therapists, nurses, and physicians, the critical care pharmacist can assist with formulating plans to target a light sedation protocol, conduct

spontaneous breathing trials (SBTs), and convert patients to agents less likely to cause respiratory depression (e.g., dexmedetomidine). The patient-centered goal is to increase the number of days the patient is alive and free of mechanical ventilation, coma, and delirium while decreasing ICU and hospital length of stay.

INITIAL MANAGEMENT OF AGITATION

Alleviate Pain

Because pain can cause agitation, and managing pain is a primary goal for ICU patients, any treatment plan intended to prevent or treat agitation should begin with assessing and treating underlying pain (Figure 2-1) (Barr 2013). In addition to managing pain, many intravenous opioids used to treat pain in critically ill patients provide sedation and dissociative effects that help prevent and treat agitation.

Nonpharmacologic Strategies

Nonpharmacologic strategies for preventing and treating anxiety and agitation rely on removing the underlying cause of agitation, providing frequent reorientation (person, place, and time), providing education and comfort, improving quality and quantity of sleep, and promoting early mobility. These strategies should be instituted before administering sedatives (Barr 2013).

Patients in the ICU have impaired and inadequate sleep cycles, and promoting sleep hygiene is a primary approach to achieving normal circadian rhythms. Sleep hygiene strategies include opening curtains/windows during the day, dimming lights at night, turning off the television at night, scheduling patient activities (e.g., phlebotomy) around intervals of protected time for sleep, and providing earplugs and eye masks at night. In addition, fatigue from mobilization may help minimize moderate to severe agitation.

If the patient or patient's family develops anxiety because of an upcoming procedure, the medical team can provide

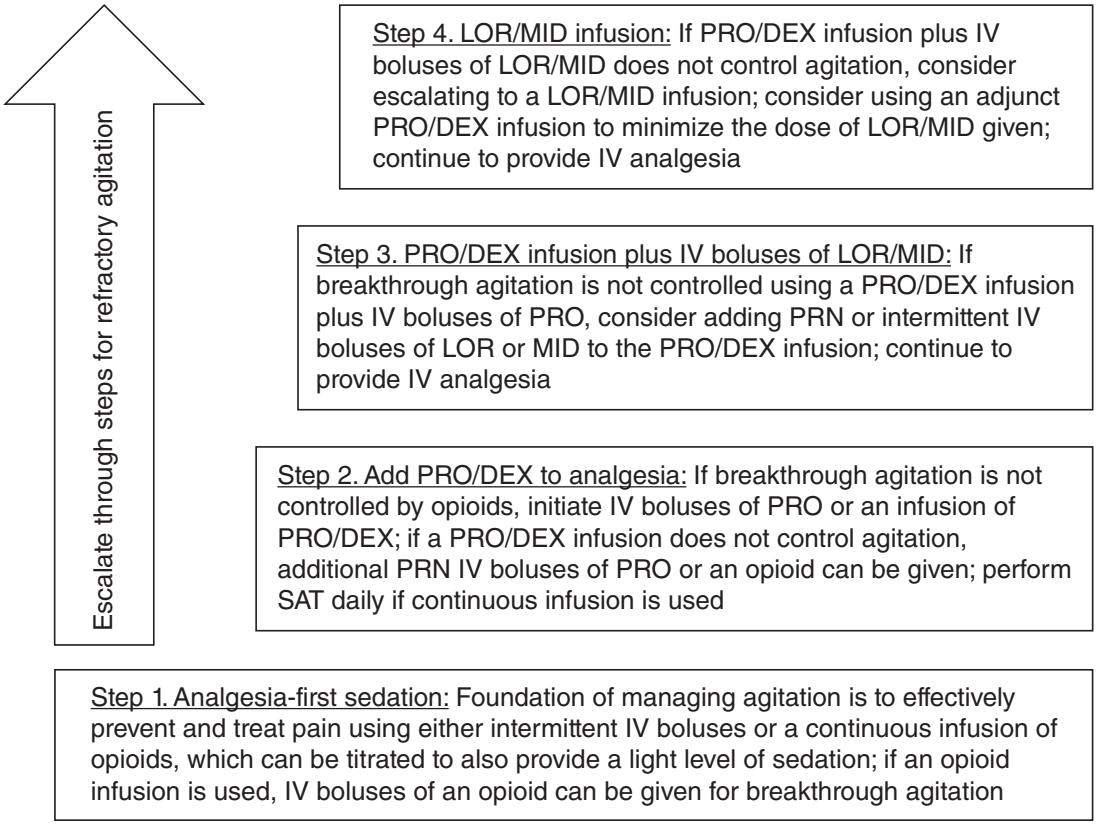

Figure 2-1. Evidence-based approach for preventing and treating agitation among mechanically ventilated adult ICU patients. Daily spontaneous breathing trials, which help promote liberation from mechanical ventilation, should be offered for all steps. Perform SATs daily for all infusions of sedatives in steps 2–4. Adequate analgesia using an opioid (usually an infusion) should be continued in steps 2–4.

/ = "or"; DEX = dexmedetomidine; IV = intravenous; LOR = lorazepam; MID = midazolam; PRN = as-needed; PRO = propofol; SAT = spontaneous awakening trial.

education to the patient and the patient's family and discuss the care plan for providing patient comfort during the procedure.

PHARMACOLOGIC AGENTS FOR AGITATION

The ideal sedation regimen should (1) adequately control pain, sedation, and anxiety; (2) have rapid onset of action; (3) have a short half-life; (4) have minimal bioaccumulation; (5) have minimal drug interactions; (6) have tolerable adverse effects; (7) be reasonable in cost; (8) be easily titrated and monitored, and (9) have evidence for routine and extended use in a variety of ICU populations (Mehta 2011). However, no single agent available on the U.S. market has all properties of an ideal sedative. A review of pharmacodynamic and pharmacokinetic properties of available sedatives is provided in Table 2-6. Indications and contraindications are provided in Table 2-7. Doses used in randomized trials of ICU sedation for mechanically ventilated ICU patients are provided in Table 2-8.

Analgesia-First Sedation Using Intravenous Opioids

Intravenous opioids commonly used for analgesia of mechanically ventilated patients include fentanyl, hydromorphone, morphine, methadone, and remifentanil. Morphine and hydromorphone can cause hypotension through a histamine-related response. Fentanyl and remifentanil are less likely to cause hypotension.

Place in Therapy

Pain is often a primary cause of agitation, and effective treatment of pain can prevent agitation. In addition to managing pain, intravenous opioids can help some patients achieve a light level of sedation without needing to initiate a hypnotic-based sedative. This approach (termed *analgesia-first sedation*) received a +2B recommendation from the 2013 SCCM PAD guidelines (Table 2-9).

Analgesia-first sedation appears to be as effective as hypnotic-based sedation for achieving an optimal level of sedation and analgesia (Breen 2005; Rozendaal 2009). Although 18%–70% of patients initially treated with

Table 2-6. Pharmacodynamics and Pharmacokinetics of Sedatives

Sedative	Predominant Mechanism of Action	Onset of Action (min)	Half-life of Parent Compound (hr)	Hepatic Clearance Through CYPs	Active Metabolites (half-life in hr)
Midazolam	$GABA_A$ receptor agonist	IV 2–5 IM inj 15	3–11	CYP3A4	α-Hydroxymidazolam (1–12, > 25 in acute renal failure)
Lorazepam	$GABA_A$ receptor agonist	IV 5–20	8–15	None	None
Diazepam	$GABA_A$ receptor agonist	IV 2–5	20–120	CYP3A4 and CYP2C19	Desmethyldiazepam (30–200) and oxazepam (3–21) (undergo urinary excretion)
Propofol	$GABA_A$ receptor agonist	IV 1–2	3–12[a]	None	None
Dexmedetomidine	α_2-Adrenergic receptor agonist	IV 15	2–3	CYP2A6	None
Ketamine	NMDA receptor antagonist	IV 1 IM inj 3–4	2	CYP2B6, CYP2C8/9, and CYP3A4	Norketamine (5.3)
Etomidate	$GABA_A$ receptor agonist	IV 1	3–6	None	None
Haloperidol	Dopamine antagonist	IV 3–20	18–54	CYP3A4 and CYP2D6	Yes, associated with extrapyramidal symptoms

[a]Half-life of propofol can be prolonged with long-term use.

GABA = γ-aminobutyric-acid; IM inj = intramuscular injection; IV = intravenous; NMDA = N-methyl-D-aspartate.

Information from: Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119-41; Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs 2012;72:1881-916; American Society of Health-System Pharmacists. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 2016; Hijazi Y. Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. Brit J Anaesth 2003;90:155-60.

Table 2-7. Indications, Contraindications, and Place in Therapy for Sedatives

Sedative	FDA-Approved Sedation-Related Indication	FDA Boxed Warnings (Pregnancy Category)	Contraindications[a]	Place in Therapy
Midazolam	Preoperative sedation (IV/IM) Procedural sedation (IV) General anesthesia (IV) Continuous sedation during mechanical ventilation (IV)	Respiratory depression Initial dose for sedation of adults should not exceed 2.5 mg and should be administered over at least 2 min (D)	Acute narrow-angle glaucoma Intra-arterial injection	ICU sedation: alternative agent ED procedural sedation: not recommended
Lorazepam	Preoperative sedation	None (D)	Acute narrow-angle glaucoma Sleep apnea syndrome Known sensitivity to polyethylene glycol, propylene glycol, or benzyl alcohol Intra-arterial injection Severe respiratory insufficiency[b]	ICU sedation: alternative agent ED procedural sedation: not recommended
Diazepam	Preoperative sedation	None (D)	Acute narrow-angle glaucoma Untreated open-angle glaucoma	ICU sedation: not recommended for continuous sedation; rarely used ED procedural sedation: not recommended
Propofol	Induction and maintenance of general anesthesia Continuous sedation during mechanical ventilation (IV)	Propofol-related infusion syndrome Tubing and unused portion should be discarded every 12 hr to prevent microbial contamination (B)	Allergy to egg products or soy products	ICU sedation: first-line agent ED procedural sedation: recommended
Dexmedetomidine	Initiation and maintenance of ICU sedation (IV), not to exceed 24 hr[c] Induction and maintenance of procedural sedation of nonintubated patients	None (C)	None	ICU sedation: first-line agent ED procedural sedation: not recommended

(*continued*)

Table 2-7. (*Continued*)

Ketamine	Sole agent for procedural sedation that does not require skeletal muscle relaxation Induction of anesthesia before giving other general anesthesia	Not reported[d] (Not reported)	Patients in whom significant elevation of blood pressure would be hazardous	ICU sedation: not recommended for continuous sedation; rarely used ED procedural sedation: recommended
Etomidate	IV induction of general anesthesia Supplementation of subpotent anesthetic agents for short operative procedures	Should only be administered by a person trained in general anesthetics Not intended for prolonged infusion because of suppression of cortisol and aldosterone production (C)	None	ICU sedation: not recommended for continuous sedation; rarely used ED procedural sedation: recommended
Haloperidol	None related to sedation	Increased mortality in older adult patients with dementia-related psychosis (C)	Severe toxic CNS depression Coma from any cause Parkinson disease	ICU sedation: not recommended for continuous sedation; rarely used ED procedural sedation: not recommended

IM = intramuscular.

[a]All products are contraindicated in patients with a known hypersensitivity reaction to that specific drug.

[b]Except for patients who are mechanically ventilated.

[c]Dexmedetomidine does not cause respiratory depression and need not be discontinued before extubation.

[d]Emergence reactions are listed as a special note in the package insert.

ICU sedation recommendations from: Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.

ED procedural sedation recommendations from: Godwin SA, Burton JH, Gerardo CJ, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med 2014;63:247-58 e18.

analgesia-first sedation will have breakthrough agitation that requires hypnotic-based sedation, analgesia-first sedation decreases overall exposure to sedatives (Breen 2005; Park 2007; Rozendaal 2009; Strom 2010). One trial reported an increased incidence of agitated delirium among patients receiving analgesia-first sedation versus propofol (20% vs. 7%, p=0.04) (Strom 2010). One quality improvement study implemented a sedation protocol that allowed for an analgesia-first approach using intermittent fentanyl boluses; a reduction was seen in the proportion of days that patients received benzodiazepines or experienced coma (Hager 2013). One trial randomized cardiac surgery patients to either an infusion of dexmedetomidine or morphine; no difference was seen in duration of mechanical ventilation or ICU stay (Shehabi 2009).

Analgesia-first sedation is associated with shorter durations of mechanical ventilation and ICU care compared with propofol or dexmedetomidine; however, patient outcomes may be similar to those with dexmedetomidine.

Benzodiazepines

Agents Available

Benzodiazepines that are available intravenously include midazolam, lorazepam, and diazepam. All three can also be given by intramuscular injection. The bioavailability of intramuscular midazolam is 90%; therefore, dose conversion between

Table 2-8. Dosing of Continuous Sedatives for Mechanically Ventilated ICU Adults

Sedative	FDA-Approved Dosing	Titration Schedule	Doses Given in Clinical Trials to Achieve Light Sedation
Midazolam	Induction: IV injection of 0.5–4 mg (0.01–0.05 mg/kg) over several minutes Maintenance: IV infusion of 1–7 mg/hr (0.02–0.1 mg/kg/hr)	Wait at least 2 min after injection doses Titrated infusion every 15–30 min	SEDCOM trial[a] Loading dose: 0.05 mg/kg was in used in 7% of patients Maintenance: Mean (-SD to +SD) 0.056 (0.028–0.084) mg/kg/hr MIDEX trial[b] Loading dose: Midazolam before randomization Maintenance: Median (IQR) 0.06 (0.04–0.10) mg/kg/hr
Lorazepam	Induction: IV injection of the smaller of 2 mg or 0.44 mg/kg[c]	Titrated infusion every 15–30 min	MENDS trial[d] Loading dose: None given Maintenance: Median (IQR) 3 (2.2–6) mg/hr
Propofol	Induction: IV injection of 10–20 mg Maintenance: Infusion of 5–50 mcg/kg/min (0.3–3 mg/kg/hr)	Titrate by 5–10 mcg/kg/min every 5–10 min	PRODEX trial[e] Loading dose: Propofol before randomization Maintenance: Median (IQR) 1.75 (1.21–2.42) mg/kg/hr
Dexmedetomidine	Induction: IV injection of 1 mcg/kg Maintenance: Infusion of 0.2–0.7 mcg/kg/hr	Titrate infusion every 30 min	SEDCOM trial[a] Loading dose: 1 mcg/kg was in used in 8% of patients Maintenance: Mean (-SD to +SD) 0.83 (0.46–1.20) mcg/kg/hr MENDS trial[d] Loading dose: None given Maintenance: Median (IQR) 0.74 (0.4–1.0) mcg/kg/hr PRODEX trial[e] Loading dose: Propofol before randomization Maintenance: Median (IQR) 0.93 (0.67–1.2) mcg/kg/hr MIDEX trial[b] Loading dose: Midazolam before randomization Maintenance: Median (IQR) 0.45 (0.27–0.76) mcg/kg/hr

[a]SEDCOM trial targeted a light-sedation goal of RASS -2 to +1 (Riker 2009).

[b]MIDEX trial targeted a light sedation goal of RASS -3 to 0 (Jakob 2012).

[c]FDA approval does not list ICU sedation for mechanical ventilation as an approved indication, and does not provide maintenance dose recommendations. The induction dose listed if recommended for procedural sedation.

[d]MENDS trial (Pandharipande 2007).

[e]PRODEX trial targeted a light sedation goal of RASS -3 to 0 (Jakob 2012).

IQR = interquartile range; N/A = not applicable; -SD = mean minus standard deviation; +SD = mean plus standard deviation.

Information from: Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53; Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; and Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.

Table 2-9. Analgesia-First Sedation and Improved Outcomes in Randomized Trials

Study	Hypnotic-Based Sedation (control arm)	Analgesia-First Sedation (intervention arm)	Difference in MV Days[a]	Difference in ICU Days[a]
(Breen 2005)	Midazolam infusion plus morphine or fentanyl infusion	Remifentanil infusion that was escalated to ≤ 2 mg IV boluses of midazolam	- 2.2 days, p=0.033	- 0.9 days, p=0.326
(Rozendaal 2009)	Propofol or midazolam infusion plus morphine or fentanyl infusion	Remifentanil infusion escalated to propofol boluses (0.2 mg/kg) or infusion	- 1.2 days[b]	- 2 days[c]
(Strom 2010)	Propofol infusion with daily interruption plus morphine boluses	IV morphine boluses of 2.5 or 5 mg escalated to a 6-hr propofol infusion	- 4.2 days, p=0.019	- 9.7 days, p=0.032

[a]Calculated as analgesia-first sedation minus hypnotic-based sedation, where a negative number represents a decrease in days for patients receiving analgesia-first sedation.

[b]Patients randomized to remifentanil were more likely to be extubated during days 1–3 of the study (p=0.02), but there was no difference for days 4–10 (p=0.95).

[c]Patients randomized to remifentanil were more likely to be discharged from the ICU during days 1–3 of the study (p=0.05), but there was no difference for days 4–28 (p=0.57).

MV = mechanical ventilation; RCT = randomized clinical trial.

Information from: Breen D, Karabinis A, Malbrain M, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Crit Care 2005;9:R200-10; Rozendaal FW, Spronk PE, Snellen FF, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. Intensive Care Med 2009;35:291-8; and Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010;375:475-80.

Table 2-10. Dexmedetomidine Infusion Rates per Clinical Trial Protocols

Multicenter, Randomized Clinical Trials	Starting Infusion Rate (mcg/kg/hr)	Upper Bound of Infusion Rate Allowable (mcg/kg/hr)
MENDS (Pandharipande 2007)	0.15	1.5
SEDCOM (Riker 2009)	0.8	> 1.1
MIDEX/PRODEX (Jakob 2012)	Not reported	1.4

Information from: Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53; Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; and Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.

intravenous and intramuscular routes is unnecessary. The onset of action for intramuscular midazolam is 10 minutes slower than for midazolam intravenous injections.

Mechanism of Action

Benzodiazepines are agonists of the α subunit of the GABA receptor ($GABA_A$) throughout the brain, which causes increased activity in the parasympathetic nervous system and overall CNS depression.

Efficacy

Benzodiazepines are extremely effective at inducing deep sedation or coma. Although patients can develop tolerance, the dose can be titrated to maintain a prolonged duration of sedation. Intravenous midazolam has the quickest onset of action (2–5 minutes) because of its water-soluble formulation and is effective for inducing sedation for procedures (e.g., RSI) or for control of breakthrough agitation (Roberts 2012).

Adverse Effect Profile

All benzodiazepines can cause respiratory depression. If severe respiratory depression occurs, respiratory support (including mechanical ventilation) should be initiated immediately. Benzodiazepine-associated respiratory depression can prevent a patient from generating spontaneous respirations and may prolong the duration of mechanical ventilation. Benzodiazepines have the potential to cause withdrawal symptoms (e.g., convulsions, hallucinations, tremor, cramps, vomiting, sweating) on discontinuation. Benzodiazepines can elicit a rare and unpredictable paradoxical reaction of agitation, restlessness, and mania. Midazolam continuous infusion should be avoided in patients with renal failure because of the accumulation of an active metabolite, α-hydroxymidazolam glucuronide.

When a lorazepam injection is given at high doses (e.g., exceeding 1 mg/kg/day), the excipient propylene glycol can cause metabolic acidosis, elevated serum osmolality greater than 320 mOsm/kg, and acute tubular necrosis (Devlin 2010; Yahwak 2008). Monitoring plasma propylene glycol concentrations is not usually possible or practical; therefore, clinicians should monitor arterial blood gas pH and calculate osmolar gap, SCr concentration, and urine output (Roberts 2012). If propylene glycol toxicity is suspected, change lorazepam to a sedative that does not contain propylene glycol and initiate supportive therapy; hemodialysis can be used in severe cases (Devlin 2010; Roberts 2012).

Place in Therapy

Because of their association with increased length of mechanical ventilation and long-term cognitive impairment, midazolam and lorazepam are no longer recommended as first-line sedatives for mechanically ventilated ICU patients. Diazepam is not recommended and is rarely used for sedation of mechanically ventilated adults because of its prolonged duration of action and active metabolites (Barr 2013).

Benzodiazepines are effective sedatives that have a rapid onset, can induce deep sedation, and can cause amnesia—desirable attributes for many clinical scenarios. Because of their quick onset of action, benzodiazepines are often used to induce sedation for procedures (including intubation) and can be used as adjuvant single bolus doses to control acute agitation in a patient who is not optimally sedated using either propofol or dexmedetomidine. In addition, benzodiazepines can suppress seizure activity, lower intracranial pressure, and alleviate symptoms of withdrawal from alcohol or chronic benzodiazepine use.

Propofol

Mechanism of Action

Propofol is a $GABA_A$ receptor agonist with anxiolytic and amnestic properties and has a rapid onset of action (1–5 minutes).

Efficacy

Propofol is a highly lipophilic phenol that rapidly redistributes out of the brain into the peripheral tissues. After a bolus injection or short infusion (e.g., 1 day of sedation), patients often wake up within 10–15 minutes of end of therapy. Clinicians should wait a minimum of 3–5 minutes to assess for efficacy between dose adjustments.

Adverse Effect Profile

Propofol causes cardiac depression (arterial hypotension and decreased cardiac output) and respiratory depression in a dose-dependent fashion; these effects are more likely to occur from bolus doses or rapid increases in infusion rates. Only 11 of the 103 study patients in the MENDS trial received open-label boluses of propofol, and the safety of as-needed propofol boluses was not evaluated (Pandharipande 2007). Because of the risk of hypotension and respiratory depression, as-needed propofol boluses may not be safe for all patients. Propofol accumulates in body tissues with longer therapies (e.g., 10 days of sedation), slowing the time to awakening after therapy ends. Propofol is formulated in an oil-in-water emulsion (1.1 kcal/mL) containing soybean oil, glycerol, and purified egg phosphatides; this formulation increases the risk of injection-site reaction, bacterial contamination, and hyperlipidemia. Up to 18% of critically ill patients receiving propofol may develop hyperlipidemia, and monitoring serum triglyceride concentrations is recommended for propofol infusions that continue more than 48 hours (Devlin 2005).

Propofol-related infusion syndrome (PRIS) is a rare but potentially fatal syndrome characterized by signs and symptoms of cardiac dysfunction (specifically, sudden-onset bradycardia that progresses to asystole), metabolic acidosis, hyperkalemia, rhabdomyolysis, hyperlipidemia, fatty infiltration of the liver, hepatomegaly, myoglobinemia/ myoglobinuria, elevated CK concentrations, and acute renal failure (Devlin 2010). This syndrome usually occurs in patients receiving higher doses (more than 5 mg/kg/hour or more than 83 mcg/kg/minute) for longer therapies (more than 48 hours) (Devlin 2005; Roberts 2012). Patients who develop ST-segment elevation or elevated cardiac enzymes while receiving a continuous infusion of propofol should also be evaluated for potential PRIS. Clinicians can monitor for PRIS by measuring serum lactate, serum triglyceride, and mixed venous oxygen saturation (Devlin 2005; Roberts 2012). If PRIS is suspected, propofol should be discontinued immediately, another sedative initiated, metabolic abnormalities corrected, and cardiovascular support provided.

Place in Therapy

Propofol can be used for induction or maintenance of anesthesia, for induction or maintenance of sedation, or for procedural sedation. The 2013 SCCM PAD guidelines list propofol as one of the first-line agents for the sedation of mechanically ventilated adult ICU patients (Barr 2013). Propofol has a rapid onset of action; it can be used for both induction and maintenance of sedation, as well as maintain a deep level of sedation (if indicated).

Dexmedetomidine

Mechanism of Action

Dexmedetomidine is a centrally acting, presynaptic α_2-adrenergic receptor agonist that decreases the release of norepinephrine and dopamine into the synaptic cleft and attenuates the sympathetic nervous system. Dexmedetomidine also has analgesic properties.

Efficacy

In the MENDS trial, patients randomized to dexmedetomidine spent more time within 1 RASS point of their sedation goal (80% vs. 64%, p=0.04) and spent more days free of delirium and coma (7 days vs. 3 days, p=0.01) than did patients randomized to lorazepam (Pandharipande 2007). In the SEDCOM trial, patients randomized to dexmedetomidine spent the same amount of time at the target of light sedation (RASS -2 to +1) as patients randomized to midazolam (77% vs. 75%, p=0.18), but they were extubated 1.9 days sooner (p=0.01) (Riker 2009). A Cochrane meta-analysis concluded that dexmedetomidine reduced the duration of mechanical ventilation and ICU length of stay for mechanically ventilated patients compared with propofol, midazolam, and lorazepam (Chen 2015). A meta-analysis of 14 randomized trials concluded that dexmedetomidine reduced the incidence of delirium, agitation, and confusion versus comparators (predominantly midazolam or propofol) (19% vs. 23%, p=0.03) (Pasin 2014).

The FDA-approved dosing for dexmedetomidine is 0.2–0.7 mcg/kg/hour; however, doses greater than 0.7 mcg/kg/hour were used in pivotal clinical trials (see Table 2-8; Table 2-10). In the SEDCOM trial, 63% of patients randomized to dexmedetomidine required open-label midazolam, and 61% of patients required average doses greater than 0.7 mcg/kg/hour (Riker 2009). In the MENDS trial, 50% of patients randomized to dexmedetomidine required average doses greater than 0.7 mcg/kg/hour (Pandharipande 2007). Because of the favorable results of these trials, clinicians should consider dosing dexmedetomidine up to 1.5 mcg/kg/hour (in patients who do not have liver failure) for more than 24 hours in combination with rescue boluses of midazolam, lorazepam, or propofol (25–50 mg) for breakthrough agitation.

Among mechanically ventilated patients who developed agitated delirium while sedated with other agents, dexmedetomidine shortens the duration of mechanical ventilation compared with placebo (multicenter randomized trial of 74 patients) and haloperidol (pilot trial of 20 patients) (Reade 2016; Reade 2009).

Adverse Effect Profile

Dexmedetomidine infusions are associated with hypotension (28%), hypertension (16%), bradycardia (7%), and xerostomia (3%). A common and dose-limiting adverse effect of dexmedetomidine is bradycardia. Initial management of dexmedetomidine-induced bradycardia is to reduce the infusion rate and reduce exposure to other concomitant chronotropic inhibitors (e.g., β-blockers). Glycopyrrolate or atropine can be used to treat symptomatic bradycardia that does not respond to tapering the dexmedetomidine dose. In patients who receive dexmedetomidine for up to 7 days, 5% have withdrawal symptoms of nausea, vomiting, and agitation within 48 hours of discontinuation. Withdrawal symptoms are uncommon for infusions lasting less than 6 hours. Initiation of clonidine, which has a similar mechanism of action, may prevent or treat symptoms of withdrawal from dexmedetomidine; however, this approach has not been evaluated in a clinical trial (Gagnon 2015).

Loading doses of dexmedetomidine have a biphasic effect on blood pressure, starting with transient hypertension (peaking 3 minutes after bolus) mediated by peripheral vasoconstriction and followed by hypotension mediated by central and peripheral sympatholytic action that can last more than 5 hours (Bloor 1992). In addition, loading doses of dexmedetomidine can cause bradycardia and decrease cardiac output, both of which peak at 3 minutes and can last more than 5 hours (Bloor 1992). Because of these hemodynamic adverse effects, loading doses are not routinely used (Dasta 2004).

Patients with Child-Pugh class A, B, and C hepatic impairment clear dexmedetomidine at rates that are 59%, 51%, and 39% those of healthy subjects. The package insert advises a dose reduction for patients with hepatic impairment but provides no specific dose adjustment. The safety of dexmedetomidine at doses greater than 0.7 mcg/kg/hour in patients with hepatic impairment is unknown because patients with severe hepatic impairment were not represented in the trials that evaluated the safety of prolonged infusions at these doses (Jakob 2012; Pandharipande 2007; Riker 2009).

Place in Therapy

The 2013 SCCM PAD guidelines consider dexmedetomidine a first-line agent for the sedation of mechanically ventilated ICU adults (Barr 2013). Dexmedetomidine does not cause respiratory depression, does not produce anterograde amnesia, maximizes the time a patient spends at a goal level light to moderate sedation, and helps create cooperative patients who can communicate their pain to nursing staff (Jakob 2012). The ability to provide light sedation without respiratory depression helps facilitate liberation from mechanical ventilation.

Dexmedetomidine as an induction agent is inferior to more rapid agents such as propofol and midazolam. Dexmedetomidine monotherapy may be unsuitable for achieving a deep level of sedation (Ruokonen 2009). In addition, dexmedetomidine has no anticonvulsive properties, which may be beneficial in the treatment of specific ICU patients. For additional information, consult an extensive review of dexmedetomidine sedation studies (MacLaren 2013).

Patient Care Scenario

A mechanically ventilated adult ICU patient (weight 96 kg) is sedated with a fentanyl infusion. The patient had three episodes of agitation (RASS 2) during an 8-hour period, and a dexmedetomidine infusion was added to the fentanyl infusion. Determine a reasonable starting dose, calculate the corresponding infusion rate (mL/hour), and develop monitoring parameters for this dexmedetomidine infusion.

ANSWER

First, establish a starting infusion rate and upper boundary infusion rate. Starting infusion doses of 0.15–0.8 mcg/kg/hour have been used in landmark clinical trials, with maximum infusion rates up to 1.4–1.5 mcg/kg/hour. A reasonable starting dose in this patient would be 0.2 or 0.4 mcg/kg/hour titrated to a light level of sedation, with a maximum infusion rate of 1.4 mcg/kg/hour.

Second, calculate an infusion drip rate. A dose of 0.4 mcg/kg/hour corresponds to 38.4 mcg/hour in this patient (weight 96 kg). The final concentration for infusing dexmedetomidine is 4 mcg/mL (400 mcg/100 mL or 200 mcg/50 mL premade bottles). A drip rate of 9.6 mL/hour provides 38.4 mcg/hour.

The most significant treatment-emergent adverse effects of a dexmedetomidine infusion are bradycardia and hypotension. Bradycardia (heart rate less than 60 beats/minute) occurs in about 20%–40% of patients and should result in a reduction in infusion rate and close monitoring. Severe bradycardia (heart rate less than 40 beats/minute) occurs in about 2%–5% of patients and would warrant discontinuing dexmedetomidine therapy and providing potential intervention with either atropine or glycopyrrolate. Hypotension (systolic blood pressure less than 80 mm Hg) occurs in about 25% of patients and should result in a reduction in infusion rate and close monitoring.

1. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53.
2. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325-9.
3. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.

Ketamine

Mechanism of Action

Ketamine blocks the *N*-methyl-d-aspartate glutamatergic receptor and induces a dissociative state and analgesic effect.

Efficacy

An average intravenous dose of 2 mg/kg generally produces 5–10 minutes of surgical anesthesia; however, the initial bolus dose can be 0.1–4.5 mg/kg and may depend on concurrent sedatives and analgesics, therapeutic goal, and clinical setting (Barr 2013). An intramuscular dose of 10 mg/kg will generally produce 12–25 minutes of surgical anesthesia. When used for analgesia, continuous infusion maintenance dosing of ketamine can be 0.05–0.4 mg/kg/hour (Barr 2013). However, appropriate continuous infusion maintenance dosing of ketamine for the sedation of critically ill patients is not clearly defined, and a wide range of doses have been reported in clinical trials (Patanwala 2015).

Adverse Effect Profile

Ketamine can cause a transient elevation in blood pressure after injection, and it is contraindicated in patients for whom a significant elevation in blood pressure would be hazardous. According to a recent meta-analysis, ketamine does not elevate intracranial pressure more than other sedatives (Roberts 2011). Ketamine can cause dissociative "emergence reactions" in 12% of patients; these rections include unpleasant hallucinations, delirium, and out-of-body experience. Concomitant use of another sedative (e.g., diazepam) may decrease the risk of emergence reactions. Limiting the physical and verbal stimulation of the patient can minimize these reactions, and severe emergence reactions can be treated with a small hypnotic dose of a short-acting or ultra–short-acting barbiturate. Although ketamine does not impair pharyngeal and laryngeal reflexes, a rapid rate of administration can cause transient respiratory depression. Ketamine can also cause hypersalivation, lacrimation, and tachycardia (Roberts 2012). Cessation of therapy after long-term use has been associated with withdrawal.

Place in Therapy

Ketamine has substantial analgesic properties and opioid-sparing properties. For prevention of agitation, it is a safe and effective agent for inducing RSI or procedural sedation (Godwin 2014). Ketamine relieves bronchospasms, which may be desirable for RSI in patients with asthma (Mace 2008). Because of its potent analgesia and dissociative properties, there may be opportunities to use ketamine in an analgesia-first approach to prevent agitation among mechanically ventilated ICU adults. However, the comparative safety and effectiveness of prolonged ketamine used in ICU patients versus other sedatives are largely unknown because of a paucity of trials (Barr 2013; Patanwala 2015).

Ketamine has a lower risk of respiratory depression and hypotension than other common sedatives, and clinicians may

consider using ketamine as an adjunctive analgesic or sedative in patients who cannot tolerate other agents because of their adverse effects. A French trial that randomized mechanically ventilated adult ICU patients to remifentanil plus either placebo or ketamine may provide useful data on the effectiveness of ketamine.

Etomidate

Mechanism of Action

Etomidate is a $GABA_A$ receptor agonist with no analgesic effect.

Efficacy

The recommended etomidate dose for inducing adults is 0.2–0.6 mg/kg (commonly 20–50 mg), with a general dose of 0.3 mg/kg injected over 60 seconds (Stollings 2014). Administering 100 mcg of fentanyl 1–2 minutes before etomidate induction may decrease the dose requirement, lessen the risk of skeletal muscle movement, and shorten the recovery period.

Adverse Effect Profile

Etomidate can cause adrenal suppression by inhibiting the enzyme that converts 11-β-deoxycortisol to cortisol; this agent has been associated with reduced cortisol and aldosterone concentrations for 6–8 hours. Although a single dose of etomidate for RSI causes adrenal insufficiency in patients with sepsis, this may not increase the risk of mortality (Gu 2015). Etomidate can cause a transient decrease in cerebral blood flow, a transient decrease in intraocular pressure, pain at the injection site (20%), and transient skeletal muscle movements (32%). Etomidate can cause a brief period of apnea (5–90 seconds) that spontaneously resolves. Etomidate can cause excitatory brain activity and should be used with caution in patients who have a history of seizures (Reddy 1993).

Place in Therapy

Etomidate's primary place in therapy is as a single-dose agent for inducing RSI or providing sedation for short procedures. Etomidate has an onset of sedation, sedation depth, and duration of effects similar to propofol (Godwin 2014). Because it inhibits the intrinsic production of cortisol and aldosterone, etomidate is not recommended for prolonged sedation. It should be used with caution in patients with sepsis or shock. Etomidate has no antiepileptic activity, and it should be used with caution in patients with a history of seizures.

Haloperidol

Haloperidol is a first-generation antipsychotic that can be administered by intravenous injection or continuous infusion (Page 2013; Reade 2009).

Adverse Effect Profile

Haloperidol can prolong the QTc interval and place patients at risk of torsades de pointes. In a pilot trial with haloperidol infusion (0.5–2 mg/hour) and QTc monitoring every 8 hours, the QTc interval was prolonged by an average of 20 milliseconds in 70% of patients (Reade 2009). A reasonable approach for safety monitoring of haloperidol is to measure the QTc during a peak concentration after steady state is reached (2–4 hours after the third or fourth scheduled dose).

Place in Therapy

A trial of 142 mechanically ventilated adult ICU patients reported no difference in the number of days free of delirium or coma between patients randomized to 2.5 mg of intravenous haloperidol or placebo every 8 hours (median days: 5 haloperidol vs. 6 placebo, p=0.53). However, scheduled haloperidol reduced the incidence of severe agitation (RASS of 2 or greater: 13% haloperidol vs. 20% placebo, p=0.008), among patients who received fentanyl (85%), propofol (85%), and midazolam (22%) (Page 2013). Because of QTc prolongation, haloperidol should not be used in patients at increased risk of torsades de pointes (grade -2C) (Barr 2013).

DELIVERY OF SEDATION

Delivery of sedation is characterized by route of administration (intravenous, intramuscular, or oral) and number of agents used (monotherapy vs. combination therapy). A 2012 Critical Care Pharmacotherapy Trials Network–supported survey of 85 ICUs reported that 60% of mechanically ventilated adult ICU patients received continuous infusion, 30% received no scheduled sedative, and 17% received scheduled bolus infusions of a sedative (Gill 2012).

Intermittent Boluses vs. Continuous Infusion

Intravenous sedation of mechanically ventilated adult ICU patients with narcotics or hypnotic-sedatives can be delivered by intermittent intravenous boluses at regularly scheduled intervals, as-needed intravenous boluses in response to breakthrough agitation, or continuous infusion (Table 2-11). Clinical trial protocols have used delivery approaches such as intravenous boluses of an opioid, continuous infusion of an opioid, continuous infusion of an opioid plus intravenous boluses of a hypnotic-sedative, and continuous infusions of both opioids and hypnotic-sedatives. During continuous infusion administration, patients are assessed, and medication is titrated often (e.g., hourly) to maintain a goal level of sedation. In addition, continuous infusions can be interrupted daily to minimize the doses provided and prevent drug accumulation.

A Cochrane meta-analysis found unclear evidence as to whether protocol-directed sedation reduces the duration of mechanical ventilation or length of ICU stay (Aitken 2015). Although no delivery strategy is clearly superior, an ideal sedation protocol minimizes the overall dose of sedative exposure (particularly benzodiazepine doses) and facilitates

Table 2-11. Doses and Frequencies of IV Boluses Used to Treat Agitation

Sedative	Scheduled Intermittent Dosing	PRN IV Dosing
Morphine	0.01–0.15 mg/kg every 1–2 hr	1–5 mg every 5–15 min (Jacobi 2002; Mehta 2012; Vasilevskis 2010)
Hydromorphone	10–30 mcg/kg every 1–2 hr	0.2–1 mg every 5–15 min (Jacobi 2002; Vasilevskis 2010)
Fentanyl	0.35–1.5 mcg/kg every 0.5–1 hr (Jacobi 2002)	25–100 mcg every 5–15 min (Jacobi 2002; Mehta 2012; Vasilevskis 2010)
Dexmedetomidine	Not given as intermittent IV boluses[a]	Not given as PRN IV boluses[a]
Propofol	Not given as intermittent IV boluses	10–20 mg for induction (package insert) 0.2 mg/kg (Rozendaal 2009) 25–50 mg for severe agitation (Pandharipande 2007)
Lorazepam	1–4 mg or 0.02–0.06 mg/kg every 2–6 hr (Carson 2006; Jacobi 2002)	1–4 mg every 5–20 min (Jacobi 2002; Mehta 2012)
Midazolam	0.02–0.08 mg/kg every 0.5–2 hr (Jacobi 2002) 1–2 mg every 15–60 min (Ruokonen 2009)	1–5 mg or 0.01–0.05 mg/kg every 5–15 min (Jacobi 2002; Mehta 2012; Riker 2009)
Haloperidol	2.5 mg every 8 hr (Page 2013)	1–5 mg every 10–20 min (Riker 2009)

[a]Dexmedetomidine IV boluses cause hemodynamic adverse effects and are not recommended for routine use in the ICU.

Information from: Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2013;1:515-23; Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92; Vasilevskis EE, Pandharipande PP, Girard TD, et al. A screening, prevention, and restoration model for saving the injured brain in intensive care unit survivors. Crit Care Med 2010;38(10 suppl):S683-91; Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; Rozendaal FW, Spronk PE, Snellen FF, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. Intensive Care Med 2009;35:291-8; Ruokonen E, Parviainen I, Jakob SM, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009;35:282-90; Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53; Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006;34:1326-32; and Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119-41.

an awake and cooperative patient who can successfully be liberated from mechanical ventilation.

It is difficult to compare the clinical outcomes associated with either continuous infusion or intermittent bolus delivery of the same sedative because of the absence or scant number of high-quality randomized trials. One single-center trial randomized patients to continuous infusion with midazolam or propofol with daily sedative interruption (n=30) or intermittent sedation (n=30). Although the number of ventilator-free days and percentage of time at the target level of sedation were similar between groups, intermittent sedation reduced the total dose of midazolam (median dose 45 mg daily interruption vs. 0 mg intermittent sedation, p<0.001) and fentanyl (median dose 1500 mcg daily interruption vs. 300 mcg intermittent sedation, p=0.004) (Nassar Junior 2014).

Introduction of a stepwise sedation protocol, which mandated the failure of intermittent boluses before a continuous infusion could be initiated, was associated with a decrease in intravenous narcotics and intravenous benzodiazepines, a lighter level of sedation, and an increase in delirium-free and coma-free days (Hager 2013). Compared with continuous

infusion sedation with daily interruptions, intermittent boluses of sedation appear to decrease total doses of narcotics and sedatives (Hager 2013; Nassar Junior 2014). However, data from a single-center retrospective study suggest that the rate of unplanned extubation is higher among patients receiving intermittent sedation (Tanios 2014). According to the current literature, a reasonable stepwise approach to minimizing the total doses of sedatives given would require the failure of sedation with intravenous boluses before escalating to a continuous infusion (Figure 2-2).

The choice of sedative may diminish the potential benefits of the delivery method. In one trial, patients randomized to continuous infusion propofol that was interrupted daily had a shorter duration of mechanical ventilation than did those receiving intermittent boluses of lorazepam (2.6 days shorter, p=0.04) (Carson 2006). This trial highlights the importance of both sedative selection and delivery method.

Monotherapy vs. Combination Therapy of Sedative-Hypnotics

Dexmedetomidine and propofol are first-line sedatives for mechanically ventilated adults. If agitation is refractory to propofol and dexmedetomidine, lorazepam and midazolam infusions may be provided as adjunctive boluses. Even when dexmedetomidine was given at doses greater than 0.7 mcg/kg/hour, 13%–63% of patients had breakthrough agitation requiring rescue boluses of propofol or midazolam (Pandharipande 2007; Riker 2009). If breakthrough agitation remains refractory to both dexmedetomidine infusion and propofol infusion, a continuous infusion of lorazepam or midazolam can be initiated. If patients are escalated to a benzodiazepine infusion, it is unknown whether keeping an adjunctive infusion of propofol or dexmedetomidine will be beneficial because this approach has not been investigated in a randomized trial.

However, patients requiring benzodiazepine infusions may benefit from being transitioned to either propofol or dexmedetomidine once they are eligible for SBTs. In one trial, patients receiving midazolam infusion and eligible for SBTs were randomized to either continue midazolam or transition to propofol; the propofol group had shorter times to extubation and shorter recovery times (Zhou 2014). A randomized trial of patients (most were sedated with a continuous infusion of propofol) who could not be extubated because of agitated delirium showed that adding a dexmedetomidine infusion, compared with placebo, shortened the duration of mechanical ventilation by 17 hours (p=0.01) (Reade 2016).

EVALUATION OF SAFETY DURING TREATMENT OF AGITATION

Respiratory Depression

A primary concern of sedation with benzodiazepines and propofol is respiratory depression. For procedural sedation of nonintubated patients, it is imperative that the clinician provide the lowest dose possible, avoid rapid administration, and be knowledgeable of the pharmacokinetics of the sedative used. Respiratory function is normally monitored using capnography, pulse oximetry, respiratory rate, and overall level of arousal (Godwin 2014). If a patient develops respiratory depression, the sedative should be discontinued, and respiratory support should be provided until the medication action dissipates.

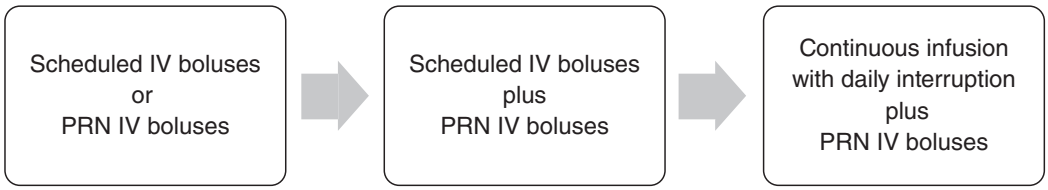

Figure 2-2. Stepwise approach to minimize the total doses of sedatives given.

A stepwise approach starts with either scheduled IV boluses or PRN intravenous boluses of preferably an opiate, or alternatively a benzodiazepine, to treat breakthrough agitation, which can be escalated to the combination of scheduled IV boluses plus PRN IV boluses. If continuous infusions are used, an opiate, dexmedetomidine, or propofol should be tried before initiating an infusion of lorazepam or midazolam. Continuous infusion sedation should be interrupted daily during SATs.

Information from: Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306; Hager DN, Dinglas VD, Subhas S, et al. Reducing deep sedation and delirium in acute lung injury patients: a quality improvement project. Crit Care Med 2013;41:1435-42; Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34; and Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.

Delirium

Benzodiazepines have a dose-dependent association with increased risk of delirium (Pandharipande 2006). Regardless of which sedative is used, a deep level of sedation and coma are associated with an increased risk of delirium (Ouimet 2007; Van Rompaey 2009). One study reported that a small portion (less than 15%) of patients may have rapidly reversible delirium that resolves after a SAT, and patients with rapidly reversible delirium may have better outcomes than patients with persistent delirium (Patel 2014).

Drug-Induced Coma

Rapid administration of sedatives or accumulation of active compounds from prolonged administration can place patients at risk of drug-induced coma. Although patients with drug-induced coma may look restful, drug-induced coma that is not medically indicated should be treated as a significant adverse event. In one multicenter prospective study, deep sedation (defined as RASS -3, -4, or -5) occurred in 71% of 259 medical/surgical ICU patients at their first sedation assessment, and early deep sedation was associated with longer durations of mechanical ventilation and higher mortality (Shehabi 2013).

Optimal identification of coma in mechanically ventilated and sedated patients requires frequent assessment of the level of sedation with a validated screening tool (RASS or SAS). Coma can be defined as a RASS of -4 or -5 or a SAS of 1 or 2 (Ely 2003; Riker 1999). If a sedated ICU patient is identified as having an unintentional drug-induced coma, current sedation therapy should be discontinued or minimized, if possible.

Post-Intensive Care Syndrome Among Survivors of Critical Illness

Post-intensive care syndrome is a constellation of health problems that plague survivors or the family of survivors of critical illness; these problems include long-term cognitive impairment (e.g., impaired memory and attention), depression, and post-traumatic stress disorder (PTSD) (Needham 2012). In one study, 34% of ICU survivors had cognitive impairment consistent with moderate traumatic brain injury 12 months after their ICU stay, and duration of in-hospital delirium was independently associated with worse global and executive cognitive function (Pandharipande 2013). Up to 37% of ICU survivors may have depression, and up to 7% may have PTSD within 12 months of ICU discharge (Jackson 2014). However, the relationship between sedation and PTSD is unclear (Treggiari 2009).

Follow-up medical consultations after ICU discharge that inform patients about their ICU stays appear to decrease the risk of PTSD (Jensen 2015). An additional opportunity to engage the patient's family is to have the family member record the events in an ICU diary that can be reviewed with the patient after discharge; this intervention decreases the risk of PTSD (Mehlhorn 2014). Care plans for preventing and treating agitation among mechanically ventilated ICU adults should be designed to minimize the risk of post-intensive care syndrome by minimizing coma and delirium, facilitating liberation from mechanical ventilation, and promoting family engagement using ICU diaries.

COORDINATING SEDATION WITH RESPIRATORY EVALUATION

The Awakening and Breathing Coordination, Delirium Monitoring and Management, and Early Mobility (ABCDE) bundle is an evidence-based, multidisciplinary approach for preventing brain dysfunction among mechanically ventilated ICU adults that is supported by high-quality, randomized trials (Ely 1996; Girard 2008; Kress 2000; Schweickert 2009; Vasilevskis 2010). Implementation of the ABCDE bundle is associated with increasing the number of days ICU patients are alive and free of mechanical ventilation, decreasing the incidence of delirium, and increasing the odds of mobilizing out of bed during ICU care (Balas 2014). Recently, this bundle has been updated to ABCDEF (Box 2-1).

The rationale behind SATs, SBTs, and choice of sedative are directly related to the provision of sedation. Pharmacists in the ICU can play an integral role in improving process measures and compliance with awakening and breathing coordination protocols (Stollings 2015).

Spontaneous Breathing Trials

The breathing component of the ABCDE bundle is based on a randomized trial demonstrating that an SBT protocol decreased the duration of mechanical ventilation by 1.5 days (p=0.003) compared with usual care without increasing complications of self-extubation or subsequent use of an invasive airway (Ely 1996). Systematic assessment of a patient's ability to produce spontaneous breaths, as well as interprofessional communication and coordination of extubation activities for eligible patients, should be a standard of care for mechanically ventilated patients.

Spontaneous Awakening Trials

The awakening component of the ABCDE bundle is based on a randomized trial showing that SATs decreased the duration of mechanical ventilation by 2.4 days (p=0.004) and duration of ICU stay by 3.5 days (p=0.02). Midazolam was used for 51% of the

Box 2-1. Components of the ABCDEF Bundle

1. Assess, prevent, and manage pain
2. Both SATs and SBTs
3. Choice of analgesia and sedation
4. Delirium assessment, treatment, and management
5. Early mobility and exercise
6. Family engagement and empowerment

Information from Society of Critical Care Medicine. ICU Liberation. [homepage on the Internet]. 2016.

patients and propofol for 49% of the patients. Total midazolam doses were cut by 46% using SATs (median total dose 426 mg vs. 230 mg, median reduction 196 mg, p=0.05), and total propofol doses were unchanged (median total dose 17,588 mg control vs. 15,150 mg intervention, p=0.54). The total morphine dose given was also reduced by 57% among patients receiving midazolam sedation (median total morphine dose: 481 mg control vs. 205 mg intervention, median reduction of 276 mg, p=0.004). A daily SAT protocol successfully reduced the total doses of sedative given, especially midazolam, and increased the percentage of days the patient was awake (9% control vs. 86% intervention, p<0.001) (Kress 2000).

Awakening and Breathing Coordination

The Awakening and Breathing Controlled (ABC) trial randomized patients to coordination of SBTs immediately after a successful SAT versus usual care and daily SBTs. Compared with the control group, patients in the intervention group had 3.1 more days alive and free of ventilation (p=0.02), 3.8 days less of ICU care (p=0.01), and 4.3 days less of hospital care (p=0.04). Intervention group patients also had a 14% absolute risk reduction in 1-year mortality (p=0.01). Most patients (more than 66%) were exposed to benzodiazepines, propofol, and opiates after enrolling in both treatment groups. Total doses of lorazepam equivalents were reduced by 49% in the intervention group (39 mg control vs. 20 mg intervention, p=0.02), and total propofol doses were unchanged (p=0.90). Although the proportion of patients who self-extubated increased in the intervention group (10% intervention vs. 4% control, p=0.03), the proportion who required reintubation was unchanged (14% intervention vs. 13% control, p=0.73) (Girard 2008).

The SLEAP trial randomized patients to protocolized sedation (control) or protocolized sedation plus daily SATs (intervention); SBTs were performed daily in both groups. The protocolized sedation was nurse-driven, and sedation needs were assessed hourly to achieve light sedation (defined as a RASS of -3 to 0 or a SAS of 3 or 4). Propofol and dexmedetomidine infusions were not permitted, and patients were sedated with benzodiazepines and opiates. The protocol provided specific instructions for tapering and discontinuing sedation drips in oversedated patients. The total midazolam dose was similar between groups (median total midazolam equivalent dose: 237 mg control vs. 222 mg intervention, p=0.91), and the average daily dose of midazolam equivalents was increased in the intervention group (mean milligrams per patient per day: 82 mg control vs. 102 mg intervention, p=0.04). This increase was driven by both higher infusion rates and bolus doses. Although the reason for the increased benzodiazepine exposure in the intervention group is unknown, the authors speculate that nurses reinitiated patients on higher doses by increasing the infusion rates. Compared with the control group, the intervention group had a similar duration of mechanical ventilation (median 7 days in both groups, p=0.52), ICU length of stay (median 10 days in both groups, p=0.36), and incidence of in-hospital mortality (30% in both groups, p=0.89) (Mehta 2012). A subgroup analysis reported that randomization to the intervention group was associated with a reduced duration of mechanical ventilation for surgical/trauma, but not medical, patients.

The SLEAP trial did not replicate the favorable outcomes of the ABC trial, which warrants some discussion. Two randomized trials of SATs, irrespective of coordination with SBTs, reduced benzodiazepine exposure by about 50% and improved patient outcomes (Girard 2008; Kress 2000). In contrast, the SLEAP trial increased benzodiazepine exposure and did not improve patient outcomes (Mehta 2012).

NON–BENZODIAZEPINE-BASED SEDATION VS. BENZODIAZEPINES FOR SEDATION OF ADULT CRITICALLY ILL PATIENTS

The four predominant sedatives used for ICU sedation can be classified as either benzodiazepines (lorazepam and midazolam) or non-benzodiazepines (propofol and dexmedetomidine). A meta-analysis of six moderate to high-quality trials concluded that benzodiazepine-based sedation was associated with a ½-day increased ICU length of stay (p=0.04) compared with non–benzodiazepine-based sedation (Barr 2013). These data led to a grade +2B recommendation to prefer sedation using non-benzodiazepines in favor of benzodiazepines (Barr 2013). A 2013 meta-analysis that included the PRODEX/MIDEX trial showed that non-benzodiazepines were associated with a 1.6-day shorter ICU length of stay (moderate quality, p<0.001) and a 1.9-day shorter duration of mechanical ventilation (moderate quality, p<0.001) but a similar prevalence of delirium (moderate quality, p=0.19) and rate of short-term mortality (low quality, p=0.88) compared with benzodiazepines (Fraser 2013). A retrospective, multicenter cohort study with a propensity-matched analysis compared propofol with either continuous infusion midazolam (2250 matched pairs) or lorazepam (1054 matched pairs) and reported that propofol was associated with decreases in mortality, duration of ICU stay, and duration of mechanical ventilation (all p≤0.001) (Lonardo 2014).

ECONOMIC EVALUATION OF SEDATION STRATEGIES

Although it may be tempting for critical care pharmacists to conduct economic evaluations of sedation from the pharmacy department perspective using only drug acquisition costs, the economic analysis is more appropriately performed from the perspective of the health care institution or third-party payer (Bioc 2014; Dasta 2010). From the institutional perspective, the durations of ICU length of stay and mechanical ventilation are the primary drivers of cost, whereas the acquisition costs of sedatives account for less than 5% of total costs (Figure 2-3) (Bioc 2014; Dasta 2010; Riker 2009).

Costs of ICU Stay and Mechanical Ventilation

An analysis of more than 50,000 ICU patients from 253 U.S. hospitals estimated the total costs per day of ICU care among nonintubated patients at $6667 for the first day of ICU care, $3496 for the second day of ICU care, and $3184 for the third or subsequent days of ICU care. This analysis also estimated the incremental cost per day of mechanical ventilation at $1522 (Dasta 2005).

Drug Acquisition Costs for Sedatives

Data analyses from randomized trials estimated the average drug acquisition costs for a total course of ICU sedation per patient at $1570 for dexmedetomidine, $161 for propofol, $82 for lorazepam, and $63 for midazolam (Bioc 2014). The differences in drug acquisition costs between dexmedetomidine and other sedatives may decrease in the future as generic dexmedetomidine formulations are approved and enter the U.S. market.

Strategies to Minimize Costs

Given that the costs of ICU care and mechanical ventilation are much higher than the drug acquisition costs for sedatives, it is apparent that sedation strategies that reduce durations of ICU care and mechanical ventilation will have the greatest impact on cost of care. Two attributes of sedation strategies have been shown to minimize costs in published clinical data: (1) choice of sedative and (2) protocols that shorten the duration of mechanical ventilation.

An economic analysis of the SEDCOM trial estimated that sedation with dexmedetomidine reduced the total cost of care by $9679 (95% CI, $2314–$17,045, p=0.01) per patient compared with midazolam. The analysis considered the costs of ICU days, days of mechanical ventilation, drug acquisition cost, and treatment of adverse events associated with sedation therapy (Dasta 2010; Riker 2009). A second economic analysis considered data from several clinical trials and concluded that despite their higher acquisition costs ($1327 non-benzodiazepines vs. $65 benzodiazepines), non-benzodiazepines were associated with much lower total ICU costs of care ($35,380 non-benzodiazepines vs. $45,394 benzodiazepines) (Bioc 2014).

A randomized trial of SBTs versus routine care found that a systematic approach to discontinuing mechanical ventilation among eligible patients effectively reduced the duration of mechanical ventilation and decreased the total costs of ICU care (median costs $15,740 intervention vs. $20,890 control) (Ely 1996). A single-center, before-and-after study showed that a PAD protocol lowered per-patient hospital costs by $869 (Awissi 2012).

CONCLUSION

Goals of sedation therapy for mechanically ventilated adult ICU patients are to prevent agitation, prevent coma, prevent delirium, maintain a goal level of sedation, prevent prolonged durations of mechanical ventilation and ICU stay, and reduce mortality. Assessing and treating pain is the

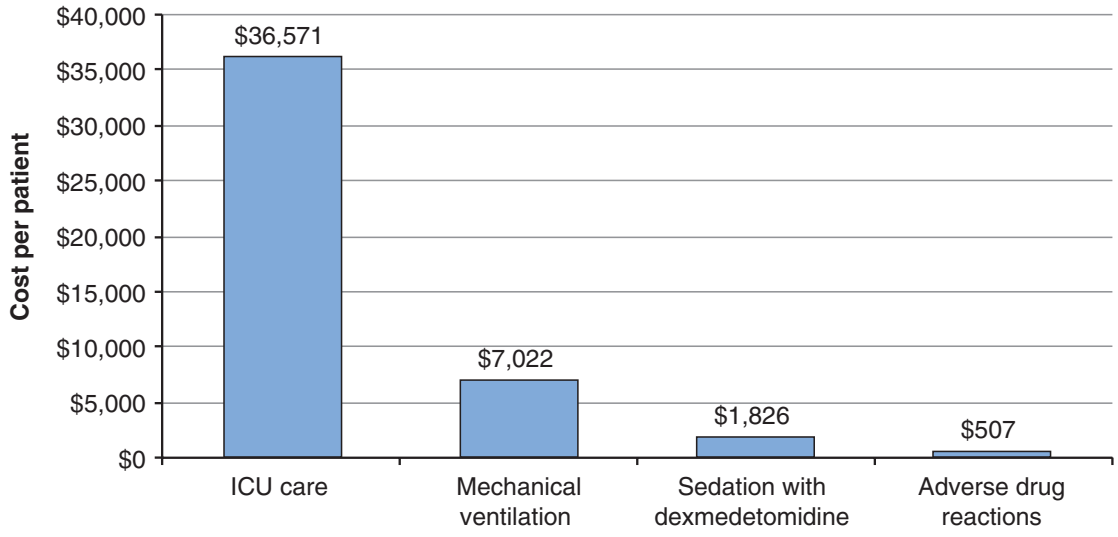

Figure 2-3. Costs per patient randomized to dexmedetomidine in the SEDCOM trial.[a]

[a]Costs are adjusted for inflation for 2007. Only data for the dexmedetomidine arm of the SEDCOM trial are shown.

Information from: Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; and Dasta JF, Kane-Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. Crit Care Med 2010;38:497-503.

Practice Points

Most critical care patients undergoing mechanical ventilation or other procedures in the ICU will require pharmacotherapy to prevent and treat agitation. However, the drugs currently used for sedation can cause short- and long-term adverse events, including prolonged duration of mechanical ventilation, delirium, long-term cognitive impairment, and death. The following practice points can help guide the clinician toward delivering pharmacotherapy using an evidence-based approach:

- **The level of sedation should be routinely measured using a valid and reliable subjective tool such as the RASS or SAS. Objective measures of electrical activity in the brain can be used to measure sedation in patients receiving neuromuscular blocking agents or to measure seizure activity.**
- **When sedation is used for mechanically ventilated ICU adults, therapy should be titrated to achieve a "light level of sedation," which some trials have defined as RASS -2 to +1 or SAS 3 to 4.**
- **Deep sedation and sedation-induced coma are associated with prolonged durations of care, cognitive impairment, and death and should be avoided. Deep sedation should only be used when light sedation is contraindicated (e.g., neuromuscular blocking agents, refractory seizures, brain injury).**
- **Pain is a primary cause of agitation, and preventing and treating pain is the first step toward managing agitation. Intravenous opioids should be given in sufficient quantities to control pain and can be titrated to achieve a light level of sedation.**
- **If intravenous opioids cannot achieve a goal level of sedation, propofol or dexmedetomidine can be initiated as the first-line sedative.**
- **Dexmedetomidine (up to 1.5 mcg/kg/hour) appears to be more effective than lorazepam and midazolam and as effective as propofol for maximizing the proportion of time patients spend at a goal level of sedation. To achieve the favorable patient outcomes seen in landmark clinical trials, most patients receiving dexmedetomidine will require doses greater than 0.7 mcg/kg/hour, and 13%–63% will require rescue boluses of other sedatives (propofol or midazolam) for breakthrough agitation. Dexmedetomidine causes bradycardia, and loading boluses are not routinely used because of hemodynamic effects.**
- **Propofol is a first-line sedative that can be given as a continuous infusion or as intravenous boluses as an adjunct to infusions of other sedatives. However, doses greater than 5 mg/kg/hour (greater than 83 mcg/kg/minute) given for more than 48 hours increase the risk of a rare and severe infusion syndrome.**
- **Lorazepam or midazolam can be used for refractory agitation; however, the doses of benzodiazepines given should be minimized.**
- **Deliver sedatives through intermittent intravenous doses, if possible. If a continuous infusion is needed, perform daily sedation interruptions, and target a light level of sedation to minimize the total dose of sedatives given.**
- **SBTs should be performed daily to facilitate early liberation from mechanical ventilation, and sedation interruption should be coordinated with the SBTs performed.**

first step in a sedation care plan. Arousal level should be monitored using valid and reliable tools. Administering sedatives should be coordinated with other activities such as performing SATs and SBTs using an interprofessional and multimodal approach (e.g., ABCDE) to awaken and animate the patient. Cooperative patients free of coma or delirium have better outcomes, and all sedative regimens should strive to achieve this patient state. If analgesics used to control pain also prevent agitation, no sedative is needed. If a sedative is needed, propofol and dexmedetomidine are first-line agents for the ICU sedation of mechanically ventilated patients.

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Self-Assessment Questions

21. You are to provide an update on ICU sedation guidelines to a group of multidisciplinary critical care colleagues. Which one of the following messages is most important to convey regarding improvements in the 2013 SCCM pain, agitation, and sedation (PAD) clinical guidelines compared with the 2002 SCCM sedation guidelines?

    A. The quality of data supporting recommendations is shown using the GRADE method.
    B. A multidisciplinary committee of experts wrote the guidelines.
    C. Guidelines were published in the official journal of the Society of Critical Care Medicine.
    D. Pharmacokinetic parameters of sedatives are clearly shown in summary tables.

22. According to the GRADE method used for the 2013 PAD guidelines, which one of the following GRADE ratings is associated with the lowest quality of evidence supporting a recommendation?

    A. -1B
    B. +1A
    C. +2B
    D. +2C

23. A 55-year-old patient with pneumonia and severe sepsis is intubated in the ED and transferred to the ICU for systemic antimicrobial treatment. Sedation is induced with a bolus of midazolam, and a dexmedetomidine infusion is initiated. The patient is also receiving an infusion of fentanyl. Which one of the following is best as the goal level of sedation for this patient?

    A. Richmond Agitation-Sedation Scale (RASS) -4 to -2
    B. RASS -2 to +1
    C. Sedation-Agitation Scale (SAS) 1–4
    D. SAS 2 or 3

Questions 24 and 25 pertain to the following case.

J.T. is a 35-year-old man with acute respiratory distress syndrome (ARDS) caused by influenza. He is mechanically ventilated through an endotracheal tube and receiving infusions of propofol, fentanyl, and cisatracurium as part of the treatment of ARDS.

24. Which one of the following tools would best monitor J.T.'s level of sedation?

    A. RASS
    B. SAS
    C. Visual analog scale
    D. Objective measure of brain function in addition to RASS or SAS

25. Which one of the following is the best goal level of sedation for J.T.?

    A. Light level of sedation to facilitate extubation
    B. Deep level of sedation because of the neuromuscular blocking agents
    C. Sedation titrated on the basis of serum concentrations of propofol and triglycerides
    D. Deep level of sedation because of the combination of fentanyl and propofol

26. An older adult patient is admitted to the surgical ICU after cardiovascular surgery on a continuous infusion of sedative. The medical team's goals for this patient are to minimize respiratory depression and facilitate rapid liberation from mechanical ventilation over the next few days. If a continuous infusion of sedation is used, which one of the following sedatives will best accomplish this goal?

    A. Dexmedetomidine
    B. Propofol
    C. Lorazepam
    D. Midazolam

27. An adult ICU patient is mechanically ventilated; a fentanyl infusion at 75 mcg/hour has effectively managed the patient's pain. Today, the patient develops acute agitation (RASS +2), which is above the target RASS range. Which one of the following would best address this first episode of acute agitation?

    A. No pharmacologic response needed because this is the first episode of agitation.
    B. Bolus 25 mg of intravenous propofol and initiate a propofol infusion at 1 mg/kg/hour.
    C. Bolus 50 mcg of intravenous fentanyl and maintain the fentanyl infusion at 75 mcg/hour.
    D. Bolus 1 mg of intravenous lorazepam and increase the fentanyl infusion to 100 mcg/hour.

28. A mechanically ventilated patient is sedated with a dexmedetomidine infusion at 0.5 mcg/kg/hour that has been titrated to a goal level of light sedation (SAS 3 or 4). The patient's pain is controlled with a fentanyl infusion at 50 mcg/hour. Which one of the following would be best to recommend as an adjunct to this dexmedetomidine infusion should this patient experience breakthrough agitation?

    A. Dexmedetomidine bolus as needed
    B. Etomidate bolus as needed
    C. Lorazepam continuous infusion as needed
    D. Midazolam bolus as needed

29. The medical team orders a dexmedetomidine infusion for an adult ICU patient receiving mechanical ventilation with normal renal and hepatic function. Pain is controlled with a hydromorphone infusion. Which one of the following dexmedetomidine titration orders is best for this patient?

    A. 1-mcg/kg bolus followed by a 0.2- to 0.7-mcg/kg/hour infusion for a maximum of 24 hours
    B. 0.2- to 0.7-mcg/kg/hour infusion for a maximum of 24 hours
    C. 0.2- to 1.4-mcg/kg/hour infusion for a maximum of 24 hours
    D. 0.2- to 1.4-mcg/kg/hour infusion with no time limit on therapy duration

30. An adult ICU patient with normal renal and hepatic function is receiving mechanical ventilation. Thirty minutes ago, the patient developed agitation (RASS +2); 25 minutes ago, the patient received a 1-mg intravenous bolus of lorazepam. The patient's current RASS score is -1. Pain is controlled with a hydromorphone infusion. This is the third episode of agitation in the past 12 hours, and the medical team orders a propofol infusion to prevent future episodes of breakthrough agitation. Which one of the following propofol infusion orders is best for this patient?

    A. Start infusion at 0.3 mg/kg/hour (5 mcg/kg/minute) titrated to 3 mg/kg/hour (50 mcg/kg/minute) with TG monitoring if infusion lasts more than 48 hours
    B. Start infusion of 0.3 mg/kg/hour (5 mcg/kg/minute) titrated to 6 mg/kg/hour (100 mcg/kg/minute) with TG monitoring if infusion lasts more than 48 hours
    C. Start infusion of 0.3 mg/kg/hour (5 mcg/kg/minute) titrated to 3 mg/kg/hour (50 mcg/kg/minute)
    D. Start bolus of 20 mg followed by a 0.3-mg/kg/hour (5 mcg/kg/minute) infusion titrated to 3 mg/kg/hour (50 mcg/kg/minute) with TG monitoring if infusion lasts more than 48 hours

Questions 31 and 32 pertain to the following case

K.N. is a 76-year-old woman (height 70 inches, weight 77 kg) admitted to the ED for septic shock secondary to a drug-resistant UTI. The patient's hypotension is refractory to fluid resuscitation. A norepinephrine infusion was initiated 30 minutes ago and is actively titrated to maintain a mean arterial pressure greater than 65 mm Hg. While in the ED, K.N. also becomes hypoxic and needs invasive mechanical ventilation support.

31. The ED physician, who has decided to provide rapid sequence intubation (RSI), will paralyze K.N. with succinylcholine. The physician wants to avoid agents that may worsen shock or lower blood pressure. Which one of the following sedation regimens is best to recommend for K.N.?

    A. Etomidate 23 mg (0.3 mg/kg) intravenous bolus given 1 minute before succinylcholine
    B. Propofol 150 mg (2 mg/kg) intravenous bolus given 1 minute before succinylcholine
    C. Ketamine 77 mg (1 mg/kg) intravenous bolus given 1 minute before succinylcholine
    D. Dexmedetomidine 77 mcg (1 mcg/kg) intravenous bolus given 1 minute before succinylcholine

32. K.N. is successfully intubated. The physician orders a continuous infusion of dexmedetomidine at a dose of 0.4 mcg/kg/hour. Dexmedetomidine will be administered using a final concentration of 4 mcg/mL. Which one of the following infusion rates is most appropriate for K.N.?

    A. 0.4 mL/hour
    B. 7.75 mL/hour
    C. 17.25 mL/hour
    D. 31 mL/hour

33. A surgical ICU patient (height 67 inches, weight 60 kg) is induced with a midazolam bolus and intubated in the operating room. The patient arrives to the ICU after surgery and is already sedated with a propofol infusion titrated to a goal RASS of -3 to 0. Over the next 6 hours, the patient has three episodes of breakthrough agitation (RASS greater than 2) that are treated with intravenous boluses of midazolam. That afternoon, the patient is escalated from propofol to a lorazepam infusion at an average rate of 5 mg/hour for the next 14 hours. The next morning, arterial blood gas and serum chemistries denote a metabolic acidosis with an anion gap. Which one of the following most likely contributed to metabolic acidosis?

    A. Uncontrolled breakthrough agitation
    B. Midazolam
    C. Propofol
    D. Lorazepam

34. A patient develops a stroke and is admitted to the ED. The stroke impairs respiratory function, and the patient is intubated and transferred to the neurological ICU for supportive care. The patient's comorbidities include stage 3 chronic kidney disease with new acute kidney injury (urine output less than 0.5 mL/kg/hour for 12 hours). Despite receiving a fentanyl infusion for analgesia, the patient has breakthrough agitation (RASS greater than 1). The physician plans to perform a neurologic examination in the morning to assess brain damage from the stroke. Given their pharmacokinetics, which one of the following sedation regimens is most likely to impair the neurologic assessment?

    A. Dexmedetomidine infusion titrated to goal level of sedation
    B. Propofol infusion titrated to goal level of sedation
    C. Midazolam infusion titrated to goal level of sedation
    D. Fentanyl infusion titrated to both control pain and achieve a goal level of sedation

35. You have been asked to develop a multimodal sedation order set that will be used as a subset of the ICU admission order set for your medical ICU. Which one of the following is best to recommend as the first step of a protocol or order set to manage ICU agitation?

    A. Effective prevention and treatment of pain
    B. Avoidance of benzodiazepine sedatives
    C. Daily use of spontaneous breathing trials (SBTs)
    D. Daily use of spontaneous awakening trials (SATs) for patients receiving a continuous infusion

36. On clinical rounds this morning, your team discusses a new patient who was transferred from another ICU. This patient has been mechanically ventilated and sedated with a midazolam infusion for 5 days. The patient was not eligible for an SBT due to deep sedation. The medical team's goal of care is to liberate the patient from mechanical ventilation. Which one of the following strategies is most likely to facilitate this patient's liberation from mechanical ventilation?

    A. Conduct SBTs daily, starting this morning.
    B. Conduct SATs daily, starting this morning.
    C. Conduct SATs paired with SBTs daily, starting this morning.
    D. Conduct SATs paired with SBTs daily, starting this morning. If the patient fails the SAT and sedation is restarted, convert midazolam to propofol.

Questions 37 and 38 pertain to the following case.

T. L. is a mechanically ventilated adult ICU patient with a recent head trauma. This morning, a SBT failed because of T.L.'s inability to generate spontaneous breaths. The medical team cannot determine whether the lack of respiratory function is because of the brain damage or the sedation therapy.

37. Which one of the following sedatives is least likely to interfere with T.L.'s SBT?

    A. Propofol
    B. Dexmedetomidine
    C. Midazolam
    D. Lorazepam

38. Which one of the following goal levels of arousal is best to liberate T.L. from mechanical ventilation?

    A. An alert and cooperative patient who can interact with the respiratory therapist
    B. Deep level of sedation to prevent ventilator-induced barotrauma
    C. Moderate level of sedation, accompanied by inadvertent brief periods of deep sedation
    D. Light sedation, accompanied by inadvertent brief periods of severe agitation

39. When discussing the costs of sedatives during formulary decisions, which one of the following factors is the main driver of total ICU costs in mechanically ventilated adults receiving sedation?

    A. Dose of sedative given
    B. Choice of sedative
    C. Treatment of sedation-related adverse drug reactions
    D. Duration of mechanical ventilation

40. Your pharmacy manager asks you to decrease the drug acquisition costs associated with sedation in your ICU. Which one of the following is the best response to this request?

    A. Limit dexmedetomidine infusions to a maximum rate of 0.7 mcg/kg/hour
    B. Implement a new sedation protocol that pairs SATs with SBTs
    C. Reduce the use of combination sedation therapy, and require clinicians to use only one sedative at a time
    D. Limit dexmedetomidine infusions to a maximum of 24 hours

Learner Chapter Evaluation: Agitation In Mechanically Ventilated ICU Patients.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

18. The content of the chapter met my educational needs.
19. The content of the chapter satisfied my expectations.
20. The author presented the chapter content effectively.
21. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
22. The content of the chapter was objective and balanced.
23. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
24. The content of the chapter was useful to me.
25. The teaching and learning methods used in the chapter were effective.
26. The active learning methods used in the chapter were effective.
27. The learning assessment activities used in the chapter were effective.
28. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

29. Distinguish among the leading guidelines regarding drug therapy recommendations for prevention and treatment of agitation.
30. Measure patient level of sedation using valid and reliable screening tools that are recommended by clinical guidelines.
31. Evaluate appropriate goals for level of sedation on the basis of patient-specific characteristics.
32. Assess the differences in pharmacologic therapies for the treatment of agitation.
33. Develop a multidisciplinary sedation care plan that is coordinated with mechanical ventilation weaning activities to minimize the duration of mechanical ventilation.
33. Evaluate sedation-related factors that contribute to total ICU costs.
34. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
35. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 36–38 apply to the entire learning module.

36. How long did it take you to read the instructional materials in this module?
37. How long did it take you to read and answer the assessment questions in this module?
38. Please provide any additional comments you may have regarding this module:

Pain and Sedation II

Pain and Sedation II Panel

Series Editors:

Bradley A. Boucher, Pharm.D., FCCP, FNAP, MCCM, BCPS
Professor of Clinical Pharmacy
Associate Dean for Strategic Initiatives and Operations
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Curtis E. Haas, Pharm.D., FCCP
Director of Pharmacy
University of Rochester Medical Center
Rochester, New York.

Faculty Panel Chair:

Amy L. Dzierba, Pharm.D., BCPS, BCCCP, FCCM
Critical Care Pharmacist, Medical Intensive Care Unit
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

Delirium and Sleep in Critically Ill Patients

Authors

Mona K. Patel, Pharm.D.
Critical Care Clinical Pharmacist, Surgical ICU
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

John W. Devlin, Pharm.D., FCCP, FCCM
Professor of Pharmacy
Northeastern University
Boston, Massachusetts

Reviewers

Eric W. Mueller, Pharm.D., FCCM, FCCP
Assistant Director, Clinical Services & Research
Department of Pharmacy
University of Cincinnati Medical Center
Adjunct Associate Professor of Pharmacy Practice
University of Cincinnati
Cincinnati, Ohio

Christina M. Agee, Pharm.D., BCPS
Critical Care Pharmacist
Pharmacy Department
Mercy Hospital NWA
Rogers, Arkansas

Sibusisiwe Gumbo, Pharm.D., BCCCP
Trauma Critical Care Pharmacist
Pharmacy Department
Mercy San Juan Medical Center
Carmichael, California

PAD Clinical Management

Author

Joanna L. Stollings, Pharm.D., FCCM, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
Department of Pharmaceutical Services
ICU Recovery Center at Vanderbilt Pharmacist
Department of Pharmaceutical Services
Vanderbilt University Medical Center
Nashville, Tennessee

Reviewers

John Papadopoulos, Pharm.D., FCCM, BCNSP, BCCCP
Director of Clinical Pharmacy Services
Critical Care Pharmacist
Pharmacy Residency Program Director
Clinical Assistant Professor of Medicine
Department of Pharmacy
NYU Langone Medical Center
New York. New York

Hesham Mourad, Pharm.D., BCPS, BCCCP
Pharmacy Informatics Team Leader
Pharmacy Department
Mayo Clinic Florida
Jacksonville, Florida

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Judy Cheng, Pharm.D., MPH, BCPS-AQ Cardiology
Professor of Pharmacy Practice
Department of Pharmacy Practice
MCPHS University
Clinical Pharmacy Specialist
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Lisa C. Hutchison, Pharm.D., MPH, FCCP, BCPS
Professor
Pharmacy Practice
University of Arkansas for Medical Sciences
Little Rock, Arkansas

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Delirium and Sleep in Critically Ill Adults

By Mona K. Patel, Pharm.D.; and John W. Devlin, Pharm.D., FCCP, FCCM

Reviewed by Eric W. Mueller, Pharm.D., FCCP, FCCM; Christina M. Agee, Pharm.D., BCPS; and Sibusisiwe Gumbo, Pharm.D., BCCCP

LEARNING OBJECTIVES

1. Demonstrate an understanding of the symptoms, epidemiology, and outcomes of delirium in critically ill adults.
2. Evaluate a critically ill adult for delirium by identifying modifiable risk factors and using a validated screening tool.
3. Design an evidence-based strategy to reduce the burden of delirium in critically ill adults.
4. Apply epidemiology and tools to evaluate sleep disruption in critically ill adults.
5. Detect modifiable factors associated with sleep disruption in critically ill adults.
6. Construct an evidence-based protocol to improve sleep quality and prevent delirium in critically ill adults.

ABBREVIATIONS IN THIS CHAPTER

BIS	Bispectral index
CAM-ICU	Confusion Assessment Method for the ICU
ICDSC	Intensive Care Delirium Screening Checklist
NREM	Non–rapid eye movement
PSG	Polysomnography
RASS	Richmond Agitation-Sedation Scale
REM	Rapid eye movement
SAT	Spontaneous awakening trial
SWS	Slow-wave sleep
TST	Total sleep time

Table of other common abbreviations.

INTRODUCTION TO DELIRIUM

Delirium is often encountered in the ICU and is associated with important short- and long-term adverse outcomes. Sleep is commonly disrupted in the critically ill population and may be associated with delirium (Pisani 2015). Several modifiable factors influence the risk of delirium and disrupted sleep in the ICU. Validated methods exist to screen for risk of delirium and evaluate sleep quality. Increasing evidence highlights the pharmacologic and nonpharmacologic interventions that may reduce the burden of delirium and disrupted sleep in critically ill adults. This chapter reviews the recent literature on delirium and disrupted sleep in the ICU, with a focus on detection methods, prevention strategies, and treatment practices to reduce the burden of these conditions on critically ill patients and their families.

DESCRIPTION OF DELIRIUM

Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness (APA 1994). The cardinal features of delirium are (1) a disturbed level of consciousness (i.e., a reduced clarity of awareness of the environment) with a reduced ability to focus, sustain, or shift attention; and (2) either a change in cognition (i.e., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance (i.e., hallucinations, delusions).

Although the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* denotes "consciousness" as "changes in attention," this minor change does not affect the validity of instruments developed for delirium recognition in the ICU. Given that level of arousal corresponds directly to level of consciousness, all patients must have an adequate level of arousal before the presence of inattention can be evaluated (EDA/ADS 2014).

Other symptoms commonly associated with delirium include sleep disturbances, abnormal psychomotor activity, hallucinations, delusions, and emotional disturbances (e.g., fear, anxiety, anger, depression, apathy, euphoria) (Marquis 2007). These delirium symptoms are often of most concern to patients, family members, and caregivers. When nonpharmacologic interventions are insufficient to treat these symptoms, pharmacologic treatment may be required. Delirium in the ICU can be denoted as either hyperactive (i.e., accompanied by agitation) or hypoactive (i.e., accompanied by lethargy), but most patients fluctuate between these two subtypes and are thus deemed to have a mixed delirium (Peterson 2006). The clinical significance of these delirium subtypes in critically ill adults remains unclear. Patients with some, but not all, of the clinical characteristics of delirium have subsyndromal delirium, a condition that may result in outcomes similar to those of delirium (Ouimet 2007).

Up to 30% of patients have delirium at the time of ICU admission (Ely 2004). Although epidemiologic studies from more than a decade ago report a delirium prevalence of up to 80% in mechanically ventilated critically ill adults, more recent investigations of this same population, when a lighter sedation target is maintained and early mobilization is routinely used, report a prevalence closer to 40% (Salluh 2015; Ely 2004). The likelihood of delirium in any ICU patient depends on both the patient's baseline risk and the patient's exposure over his or her ICU stay to precipitating risks and medical factors (Zaal 2015b). For example, medical patients have a higher incidence of delirium than surgical patients (Van Rompaey 2009).

Delirium related to either drug or alcohol withdrawal, which usually manifests as the hyperactive form, has a pathophysiology distinct from other causes of delirium; this type of delirium is not reviewed here (Barr 2013).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Appropriate evaluation and treatment of pain in the critically ill population
- Appropriate assessment and management of agitation and anxiety in the critically ill population

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Society of Critical Care Medicine (SCCM). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU. Crit Care Med 2013;41:263-306.
- SCCM. ICU Liberation Collaborative [homepage on the Internet].
- Vanderbilt University Medical Center. ICU Delirium and Cognitive Impairment Study Group [homepage on the Internet].

IMPACT OF DELIRIUM ON PATIENT OUTCOME

Delirium, as a manifestation of acute brain dysfunction, is associated with several undesirable ICU outcomes including self-extubation, increased duration of mechanical ventilation and length of ICU stay, and higher ICU mortality (Salluh 2015). The trajectory of a patient's severity of illness over the course of an ICU admission influences the relationship between delirium occurrence and ICU mortality (Klein Klouwenberg 2014). Delirium also increases both hospital and longer-term (e.g., 6 months) mortality. The number of ICU days spent with delirium affects 6- and 12-month mortality; therefore, the use of strategies shown to reduce the number of ICU days spent with delirium is an important goal for ICU clinicians (Salluh 2015).

Patients who develop delirium in the ICU are more likely to transition to a skilled nursing facility (e.g., nursing home) than to a rehabilitation facility or home (Salluh 2015). Delirium may lead to cognitive impairment 6 months after ICU discharge that is similar in severity to that observed with moderate dementia or a traumatic brain injury (Pandharipande 2013). These cognitive deficits often persist for weeks or months, or never resolve at all, and often delay the patient's ability to resume precritical illness activities and function. Patients with ICU delirium have a greater incidence of depression and commonly have prolonged sleep abnormalities (Pisani 2015; Jackson 2014).

The burden of delirium can have profound effects on spouses and family members, particularly if they are required to assume a caregiver role on a consistent basis. Given that delirium effects often persist long after ICU discharge, it is now recognized as a major public health problem that costs the United States up to $16 billion each year (Barr 2013).

PATHOPHYSIOLOGY OF DELIRIUM IN THE ICU

Although the study of delirium in the critically ill population has greatly expanded in the past 15 years, the underlying pathophysiology of delirium in this population remains poorly

understood. Metabolic pathways postulated to cause delirium include inflammation, neurotransmitter dysfunction, ischemia, glucose dysregulation, disruption of the hypothalamic-pituitary axis, and tryptophan metabolism. However, our understanding of how these mechanisms interact to cause a delirium state remains limited (Table 1-1).

Establishing the pathogenesis of delirium is challenging, given that delirium likely occurs through a complex interplay involving different systems and mechanisms; this is further confounded by critical illness itself, which is a dynamic, ever-changing process. Moreover, a valid animal model for delirium has yet to be developed, and neither imaging techniques nor biomarkers are valid ways to predict or identify delirium in the ICU. All mechanistic-focused delirium studies in the ICU setting still rely on a symptom-based diagnosis of delirium using bedside clinical assessment tools (AGS/NIA 2015).

RECOGNITION OF DELIRIUM IN THE ICU

Given the multifactorial and fluctuating nature of delirium, a cursory "one-time-only" bedside evaluation without the use of a validated screening tool is an ineffectual strategy to identify delirium (Pun 2013). Delirium is challenging to recognize in the ICU setting because most patients are intubated and cannot verbally communicate, the use of drugs that reduce level of consciousness is prevalent, hypoactive delirium is common, and patients may be too unstable to participate in lengthy assessments (Devlin 2007). However, the ability to accurately recognize delirium is a key component when developing interprofessional strategies focused on reducing reversible causes and initiating associated treatment strategies (Barr 2013).

The ideal delirium screening tool combines high sensitivity (i.e., will be positive when delirium is present) and high specificity (i.e., will be negative when delirium is not present). Among the ICU delirium screening tools developed, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) have the greatest psychometric strength (Barr 2013; Bergeron 2001; Ely 2001). Two recent meta-analyses highlight the robust data that support using the CAM-ICU or the ICDSC in ICU clinical practice (Gusmao-Flores 2012; Neto 2012). An important caveat, however, is their limited utility in neurologic injury because the specificities of both tools are low among patients with moderate traumatic brain injury (Frenette 2016).

Patients who are deeply sedated (i.e., Richmond Agitation-Sedation Scale [RASS] score of -4 or less or Sedation-Agitation Scale score of 2 or less) cannot be evaluated with the CAM-ICU or the ICDSC until they are more awake (Pun 2013). Patients receiving continuous sedation should be evaluated for delirium after a spontaneous awakening trial (SAT). Delirium that is recognized before the SAT is likely to be rapidly reversible and not clinically significant (Patel 2014b). It is recommended that delirium screening be performed several times daily (at least twice) given the fluctuating nature of delirium. Additional assessments are recommended when changes in mental status occur (Pun 2013).

RISK FACTORS FOR DELIRIUM

Over the past decade, much research has focused on better elucidating the aspects of delirium in the ICU that are predictable, preventable, detectable, and treatable (Zaal 2015b). A critically ill patient's risk of delirium depends on a complex

Table 1-1. Proposed Mechanisms for Delirium and Potential Inciting Factors

Delirium Mechanism	Inciting Causes
Cholinergic activation	Alcohol withdrawal, medications (e.g., neostigmine, nicotine)
Cholinergic inhibition	Medications (e.g., diphenhydramine), critical illness
Cortisol excess	Cushing syndrome, glucocorticoids, stroke, surgery
Cytokine excess	Conditions like sepsis that lead to IL-1β, IL-6, TNFα excess
Dopamine activation	Medications (e.g., amantadine, levodopa), stroke
GABA activation	Alcohol and benzodiazepine withdrawal, hepatic failure
Glutamate activation	Alcohol withdrawal, hepatic failure
Serotonin activation	Medications (e.g., olanzapine, serotonin reuptake inhibitors), substance withdrawal
Serotonin deficiency	Medical illness, surgical illness

GABA = γ-aminobutyric acid; IL = interleukin; TNF = tumor necrosis factor.

Information from: Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 1999;54:B239-46.

interplay between predisposing and precipitating risk factors. Given the current paucity of data on the effect of treatment options for delirium, clinicians should focus their efforts on preventing delirium as soon as the patient is admitted to the ICU, with emphasis on potentially modifiable risk factors (Trogrlić 2015; Barr 2013). Early recognition and management of these factors should constitute the foundation of all delirium prevention programs in the ICU.

Modifiable vs. Non-modifiable Risk Factors

Recent studies have explored the risk factors for delirium in the ICU; for many of these studies, however, the methodologic rigor is poor, the patient case mix is variable, and the method and intensity of delirium evaluation are less than ideal (Zaal 2015b). Although cohort studies evaluate association, only randomized controlled studies define causality (Mehta 2015).

A recent systematic review of risk factors for delirium in the ICU included only high-quality studies and incorporated appropriate multivariate modeling. More than 1000 studies were initially identified and 90 potential ICU delirium risk factors were considered; however, only 33 high-quality studies were included in the final review. The authors found only 11 putative risk factors for delirium to be supported by either a strong or a moderate level of evidence (Table 1-2) (Zaal 2015). The SLEAP study was not considered in this review but is important to consider given its randomized design; an evaluation of its data found the following modifiable antecedent factors to be independently associated with delirium onset: restraint use, antipsychotic administration, and midazolam dose administered (Mehta 2015).

Although baseline risk factors for delirium (i.e., factors present at the time of ICU admission) are generally not modifiable, many environmental and drug-related factors associated with increased risk of delirium are often reversible (Zaal 2015b; Barr 2013). The nonpharmacologic reversible factors of greatest importance include patient immobilization; application of restraint; excessive ambient noise; and lack of windows, clocks, or other environmental features conducive to maintaining orientation and circadian normalcy. For strong and moderate risk factors for delirium, see Table 1-2.

Drug-Associated Delirium

Many medications used in the ICU may cause or worsen delirium (Table 1-3). Factors that predispose patients to drug-induced delirium include (1) number of deliriogenic agents administered (e.g., greater than 3); (2) pharmacokinetic derangements, possibly associated with aging, organ dysfunction, or drug interactions; (3) medical comorbidities associated with impaired integrity of the blood-brain barrier (e.g., dementia, stroke); and (4) use of psychoactive drugs (Devlin 2011b). Suggested mechanisms for drug-induced delirium include an excess of dopamine, norepinephrine, and glutamate release, together with both increased and decreased serotonergic and γ-aminobutyric acid (GABA) activity (Flacker 1999). The diagnosis of drug-induced delirium is challenging and is usually one of exclusion that is based on the appearance (and resolution) of delirium relative to medication use.

Given that drug exposure, many non-drug delirium risk factors, and the presence of delirium itself vary over each day that a patient spends in the ICU, complex, time-dependent models are needed to evaluate the association between medication exposure and delirium occurrence (Devlin 2014). Thus, more time-dependent, multivariate analyses have been published, incorporating Markov models focused on evaluating the association between drug exposure (e.g., benzodiazepines, corticosteroids, anticholinergics) and the daily odds of transitioning from an awake and non-delirious state to delirium the next day (Kamdar 2015; Wolters 2015a, 2015b; Zaal 2015a; Schreiber 2014; Pandharipande 2006).

Table 1-2. Risk Factors for Delirium

	Strong Risk Factors	Moderate Risk Factors
Non-modifiable	• Older age • History of dementia • Pre-ICU emergency surgery or trauma • Higher severity of illness • Need for mechanical ventilation • Sepsis • Metabolic acidosis	• Alcohol consumption • Hypertension • Moderate cognitive impairment • Admission with infection or respiratory insufficiency • Medical admission
Modifiable	• Iatrogenic coma • Benzodiazepine use • Restraint use • Patient immobility	• Opioid use • Antipsychotic use • Excessive ambient noise • Admission to an ICU room lacking features to help maintain orientation and circadian normalcy • Living alone (older adult)

Table 1-3. ICU Medications Commonly Associated with Delirium

Category of Medication	Examples	Mechanism
Analgesics	Fentanyl	GABA antagonism
	Hydromorphone	GABA antagonism
	Morphine	GABA antagonism
	NSAIDs	Anticholinergic activity
Anti-infectives	Acyclovir	Unknown
	Amphotericin	Unknown
	Cefepime	GABA antagonism
	Linezolid	Serotonergic dysfunction
	Macrolides	Unknown
	Quinolones	GABA antagonism
	Voriconazole	Unknown
Anticholinergics	Atropine	Anticholinergic activity
	Benztropine	Anticholinergic activity
Anticonvulsants	Levetiracetam	Unknown
Antidepressants	Serotonin release inhibitors	Serotonergic dysfunction
Antihistamines	Diphenhydramine	Anticholinergic activity
Cardiac medications	α-Blockers	Anticholinergic activity
	Amiodarone	Anticholinergic activity
Antipsychotics	Haloperidol	Anticholinergic activity
	Olanzapine	Anticholinergic activity
Corticosteroids	Dexamethasone	Anticholinergic activity
	Hydrocortisone	Anticholinergic activity
	Methylprednisolone	Anticholinergic activity
Dopaminergics	Amantadine	Excess dopaminergic activity
	Bromocriptine	Excess dopaminergic activity
Prokinetics	Metoclopramide	Excess glucocorticoid activity
Sedatives	Ketamine	NMDA antagonism
	Lorazepam	GABA agonism
	Midazolam	GABA agonism
	Propofol	GABA agonism

GABA = γ-aminobutyric acid; NMDA = *N*-methyl-D-aspartate.

Information from: Devlin JW, Fraser GL, Riker RR. Drug-induced coma and delirium. In: Papadopoulos J, Cooper B, Kane-Gill S, et al, eds. Drug-Induced Complications in the Critically Ill Patient: A Guide for Recognition and Treatment. Chicago: Society of Critical Care Medicine, 2011:107-16.

A dose-related association between benzodiazepine exposure and a daily transition to delirium has been reported in several investigations; however, a recent analysis failed to show an association between anticholinergic drug exposure and a daily transition to delirium (Kamdar 2015; Wolters 2015b; Zaal 2015a; Pandharipande 2006). One analysis of patients with acute lung injury (ALI) found that exposure to corticosteroid therapy was associated with greater odds of transitioning to delirium, but a much larger analysis of critically ill adults both with and without ALI showed no such association (Wolters 2015a; Schreiber 2014). Although the results of studies like these suggest that the association between a specific drug

class and delirium is likely very low, they cannot definitively declare that an association does not exist, particularly when considered among other factors within a multivariate model.

If use of an "at-risk" drug cannot be avoided, the lowest possible dose should be prescribed for the shortest duration possible (Devlin 2011b). Common strategies to reduce medication-associated delirium are presented in Box 1-1.

DELIRIUM PREVENTION

Given that many risk factors for ICU delirium may be modifiable, a careful preemptive evaluation of the environmental and drug-related risk factors should be conducted and active prevention strategies initiated, as appropriate, for all critically ill patients (Trogrlić 2015; Barr 2013).

Nonpharmacologic Strategies

The evidence for using nonpharmacologic delirium prevention strategies in the critically ill population is far stronger than the evidence available to support using pharmacologic prevention strategies (Barr 2013). Early patient mobilization, which can only be completed in patients who are awake, reduces both the incidence and the duration of delirium while significantly increasing the likelihood that patients will return to their pre-ICU functional state on hospital discharge (Schweickert 2009). Frequent reorientation and daytime environmental stimulation also reduce the incidence of delirium (Colombo 2012). Efforts that target sleep normalcy are discussed in the sleep section of this chapter.

Box 1-1. Strategies to Reduce Medication-Related Delirium in the ICU

- Avoid polypharmacy and ensure medication dosing is appropriate
- Consider medication withdrawal effects (particularly benzodiazepines)
- Avoid anticholinergic medications, when possible
- Avoid benzodiazepines, when possible (including sleep aids)
- Avoid use of non-benzodiazepine sleep aids, when possible
- Use the lowest effective corticosteroid dose
- Use the lowest effective opioid dose to control pain/optimize non-opioid analgesic
- Avoid metoclopramide, when possible
- If delirium occurs with levetiracetam, consider other anticonvulsant options
- Reassess need for continued antibiotic therapy
- Monitor diuretic therapy for signs of dehydration and/or electrolyte abnormalities

Information from: Devlin JW, Fraser GL, Riker RR. Drug-induced coma and delirium. In: Papadopoulos J, Cooper B, Kane-Gill S, et al, eds. Drug-Induced Complications in the Critically Ill Patient: A Guide for Recognition and Treatment. Chicago: Society of Critical Care Medicine, 2011:107-16.

Pharmacologic Strategies

The 2013 Society of Critical Care Medicine pain, agitation, and delirium guidelines do not advocate pharmacologic intervention to prevent delirium (Barr 2013). Because sedative-induced coma is an important risk factor for delirium, strategies focused on maintaining patients in an awake (or lightly sedated) state such as SAT or protocolized sedation must be used (Barr 2013). Currently, no agent has FDA label approval for the prevention of delirium in critically ill patients. In a randomized, placebo-controlled pilot study of 68 critically ill, mechanically ventilated adults with subsyndromal delirium in the first 48 hours of ICU admission, the administration of haloperidol 1 mg intravenously every 6 hours did not prevent transition to delirium and was associated with greater safety concerns, including excessive sedation and QTc prolongation (Al-Qadheeb 2016). A well-designed but underpowered multicenter, randomized controlled trial of delirium prophylaxis with either haloperidol or ziprasidone found no benefit with either treatment group compared with placebo (Girard 2010).

Other randomized studies have evaluated a drug-based delirium prophylaxis strategy but only in patients undergoing a surgical procedure (primarily elective); these patients generally have a short duration of postsurgical ICU care (Serafim 2015). No evidence suggests that the perioperative use of dexmedetomidine prevents delirium in the ICU. In the largest ICU delirium pharmacologic prophylaxis study published to date, a low-dose infusion of haloperidol administered for 12 hours after major abdominal surgery reduced the incidence of delirium from 23% to 15% (p=0.03) (Wang 2012). However, the severity of illness of these patients was generally low, and most spent less than 24 hours in the ICU. Further research regarding the safety and efficacy of both dexmedetomidine typical and atypical antipsychotics is currently under way.

DELIRIUM TREATMENT

Removing or reducing delirium risk factors is the most important strategy when resolving delirium symptoms and limiting the associated sequelae (Trogrlić 2015; Barr 2013). Mnemonics such as ICUDELIRIUMS can help recall the common risk factors and causes of delirium in the ICU when evaluating a patient (Table 1-4).

Eight prospective, randomized studies have evaluated various drugs to treat delirium in critically ill patients (Table 1-5). The impact of each potential delirium-reducing intervention was reported in one or more of four different ways: (1) presence of delirium at the end of treatment period (n=4), (2) time to delirium resolution (n=3), (3) duration of delirium (n=3), and (4) severity of delirium (n=1).

Antipsychotics

Of the four studies evaluating the efficacy of an antipsychotic agent for the treatment of delirium (Page 2013; Devlin 2010; Girard 2010; Skrobik 2004), only one showed a difference in

Table 1-4. ICU DELIRIUM(S) Mnemonic

Iatrogenic exposure	Diagnostic procedures, therapeutic interventions, or a harmful occurrence deemed an unnatural consequence of the patient's illness
Cognitive impairment	Preexisting dementia, stroke, or depression
Use of restraints and catheters	Avoid use of restraints and bladder catheters unless clinically indicated
Drugs	Sedatives (e.g., benzodiazepines) and medications with anticholinergic activity Abrupt cessation of smoking or alcohol Withdrawal from chronic sedative use
Elderly	Patients > 65 years
Laboratory abnormalities	Hyponatremia, azotemia, hyperbilirubinemia, hypocalcemia, metabolic acidosis
Infection	Sepsis Urinary or respiratory tract infections
Respiratory	Respiratory failure (PCO_2 > 45 mm Hg, PO_2 < 55 mm Hg, or SAO_2 < 88%) COPD, ARDS, PE
Intracranial perfusion	Presence of hypertension, hypotension, hemorrhage, stroke, or tumor
Urinary/fecal retention	Urinary retention or fecal impaction, especially in older adult and postoperative patients
Myocardial	Myocardial causes including myocardial infarction, acute heart failure, and arrhythmia
Sleep and Sensory deprivation	Alterations of the sleep cycle and sleep deprivation Nonavailability of glasses or hearing devices

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism.

outcomes (Devlin 2010). In this small pilot study, patients with delirium treated with intermittent haloperidol were randomized to additionally receive either quetiapine 50 mg or placebo every 12 hours. All patients were allowed to receive haloperidol 1–10 mg every 2 hours as needed. The quetiapine dose was increased by 50 mg if more than one haloperidol dose was given in the previous 24 hours. The main study finding was that delirium resolved faster in patients administered quetiapine and resulted in a decreased duration of delirium. The study had many limitations, including its small size and the fact that all patients in the placebo group received one or more intravenous doses of haloperidol. Evidence therefore remains weak to support the routine use of antipsychotic therapy for the treatment of delirium in any ICU patient population, particularly for ICU patients with delirium who are not acutely agitated (Serafim 2015; Barr 2013).

Despite a relative lack of evidence to support the use of an antipsychotic agent to manage delirium—as well as recent ICU practice guidelines that only weakly recommend their use—antipsychotics are commonly administered to patients with either proven or suspected ICU delirium (Devlin 2011a; Patel 2009). Reasons for this include clinician belief that delirium is dominantly a neurotransmitter-mediated process, greater familiarity with older delirium guidelines that advocate for antipsychotic use, the challenge of managing agitation in a patient with delirium, and underappreciation of the risks associated with these agents.

Sufficiently powered, carefully designed, multicenter trials that incorporate a true placebo arm are needed to address the hypothesis that antipsychotics are beneficial in the treatment of delirium in critically ill patients. More recently, it has been suggested that delirium treatment studies should focus on evaluating the effect of antipsychotic therapy on the outcomes that are of greatest importance to patients, such as duration of mechanical ventilation, length of hospitalization, and functional status after discharge.

Dexmedetomidine

Four large, randomized studies compared dexmedetomidine and benzodiazepine sedation strategies (Jakob 2012; Riker 2009; Ruokonen 2009; Pandharipande 2007). Of these, two that evaluated the presence of delirium each day and included midazolam infusions found that patients receiving dexmedetomidine were less likely to have delirium at the end of therapy (Riker 2009; Ruokonen 2009). Conversely, a randomized study comparing dexmedetomidine with lorazepam showed no difference in the presence of delirium or delirium-free days, but a subanalysis of the patients with sepsis

Table 1-5. Study Data on Antipsychotic or Dexmedetomidine to Treat Delirium in the Critically Ill

Author (yr)	Baseline Delirium (%)	Patient Population (%)	Intervention	Control	Delirium Present at End of Study Period (%)	Duration of Delirium
Skrobik (2004)	100	Surgical = 95; intubated = 0	Olanzapine 5 mg PO/ENT daily (n=28)	Haloperidol 2.5–5 mg PO/ENT q8hr (n=45)	NR	NR
Pandharipande (2007)	61	Medical = 70; intubated = 100	Dexmed up to 1.5 mcg/kg/hr (n=52)	Lorazepam up to 10 mg/hr (n=51)	79 vs. 82; p=0.65	Delirium-free days 9 (5–11) vs. 7 (5–11); p=0.09
Ruokonen (2009)	NR	Medical = 53; intubated = 100	Dexmed up to 1.4 mcg/kg/hr (n=41)	Midazolam up to 0.2 mg/kg/hr or propofol up to 66 mcg/kg/min (n=44)	44 vs. 25; p=0.035	NR
Riker (2009)	60	Medical = 86; intubated = 100	Dexmed up to 1.4 mcg/kg/hr (n=244)	Midazolam up to 0.1 mg/kg/hr (n=122)	54 vs. 77; p<0.001	NR
Devlin (2010)	100	Medical = 75; intubated = 81	Quetiapine up to 200 mg PO/ENT q12hr (n=18)	Placebo PO/ENT (n=18)	NR	36 (12–87) vs. 120 (60–195) hr; p=0.006
Girard (2010)	49	Medical = 62; intubated = 100	Ziprasidone 40 mg PO/ENT up to q6hr (n=30)	C1: Haloperidol 5 mg PO/ENT q6hr (n=35) C2: Placebo IM/PO/ENT (n=36)	69 vs. 77; p=0.28	4 (2–7) vs. 4 (2–8) [C1] vs. 2 (0–5) [C2] days; p=0.93
Page (2013)	NR	Medical = 65; intubated = 100	Haloperidol 2.5 mg IV q8hr (n=71)	Placebo IV (n=70)	NR	5 (2–8) vs. 5 (1–8) days; p=0.53
Reade (2016)	100	Medical = 41; intubated = 100	Dexmed up to 1.5 mcg/kg/hr (n=39)	Placebo IV (n=32)	NR	Time to resolution 23 (13–54) vs. 40 (25–76) hr; p=0.01

Data presented as median (interquartile range); Dexmed = dexmedetomidine; ENT = enterally; IM = intramuscular; IV = intravenous; NR = not reported; PO = by mouth; q = every.

Information from: Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004;30:444-9; Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53; Ruokonen E, Parviainen I, Jakob S, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009;35:282-90; Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99; Devlin JW, Roberts R, Fong JJ, et al. Efficacy and safety of quetiapine for delirium in the ICU: a randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010;38:419-27; Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010;38:428-37; Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2013;1:515-23; and Reade MC, Eastwood GM, Bellomo R, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016;315:1460-8.

showed that patients receiving dexmedetomidine had more delirium-free days (Pandharipande 2010).

Together, these data are inconclusive about whether benzodiazepine use raised, reduced, or had a mixed effect on the risk of delirium. Therefore, further investigations are needed. Because of evidence showing an increased risk of delirium with benzodiazepine use, dexmedetomidine should be used instead for sedation in patients with agitated delirium not caused by uncontrolled pain. In a small, potentially underpowered study of mechanically ventilated patients with agitated delirium, the use of dexmedetomidine, rather than a haloperidol infusion, did not help resolve delirium more rapidly (Reade 2009). However, in one randomized, placebo-controlled trial of mechanically ventilated patients with agitated delirium, dexmedetomidine, when instituted to treat agitated delirium, was associated with a faster resolution of delirium and fewer days spent mechanically ventilated (Reade 2016). The results of this recent study suggest that for ICU patients with delirium, dexmedetomidine should also be considered in patients with persistent agitation despite addressing underlying causes for agitation (e.g., withdrawal), mitigating modifiable risk factors for delirium, and treating with intermittent doses of antipsychotics.

Cholinesterase Inhibitors

One multicenter, randomized, placebo-controlled study that evaluated rivastigmine for the treatment of delirium was terminated early because rivastigmine was associated with higher mortality (van Eijk 2010). In addition, there was a trend toward a longer duration of delirium with the use of rivastigmine. As such, cholinesterase inhibitors should not be used to prevent or treat delirium in any ICU patient population, but it is reasonable to continue their use in patients treated for Alzheimer disease before ICU admission (Barr 2013).

Valproic Acid

In a patient who cannot tolerate oral/enteral therapy, particularly if the use of intravenous haloperidol is precluded by a prolonged QTc interval, intravenous valproic acid may be considered. When administered as a 500-mg intravenous load followed by 50–100 mg intravenously every 6 hours, valproic acid has reduced delirium-associated agitation (Sher 2015).

INTRODUCTION TO SLEEP

Critically ill adults often have disrupted sleep and circadian rhythm alterations. Sleep dysfunction is associated with several unwanted physiologic consequences and may increase the risk of delirium. This section reviews the ways in which sleep is altered in the critically ill population, how sleep can be evaluated in the ICU, the key factors that alter sleep in this population, and pharmacologic and nonpharmacologic strategies that can improve the outcomes for adults with disrupted sleep in the ICU.

Characterization of Sleep in Healthy vs. Critically Ill Adults

The sleep-wake cycle largely depends on coordination between sleep-wake homeostasis (also known as *process S*)

Patient Care Scenario

A 45-year-old man is admitted to the surgical ICU after undergoing a liver transplant. His infusions on ICU admission include propofol 30 mcg/kg/minute, fentanyl 50 mcg/hour, norepinephrine 10 mcg/minute, and vasopressin 0.04 unit/minute. His RASS is -5, and his Critical-Care Pain Observation Tool (CPOT) score is 2, indicating a lack of moderate-severe pain. On surgical ICU day 2, his fentanyl and propofol infusions are discontinued, and he is extubated. He is initiated on a corticosteroid taper for his immunosuppression and a hydromorphone patient-controlled analgesia for pain control. His RASS is -1, and he expresses mild pain of 3 using the numeric rating scale. In the afternoon, he is lethargic and appears confused, but his CAM-ICU score is negative. The medical team worries that he is at high risk of developing delirium. Which one of the following would best prevent delirium in this patient?

ANSWER

Prevention strategies, both pharmacologic and nonpharmacologic, should be implemented in all critically ill patients. The evidence for nonpharmacologic strategies for prevention of delirium is stronger than that for pharmacologic strategies and includes early mobilization, frequent reorientation and daytime stimulation, and minimization of sleep disruption (e.g., noise and light reduction at night, bundling of patient care activities, earplugs, eye masks). No drugs can be recommended for the prevention of delirium at this time. However, avoiding iatrogenic coma and keeping the patient more awake are important for delirium prevention in the ICU.

This patient should undergo early mobilization and frequent reorientation. In addition, every effort must be made to ensure that he gets adequate and restful sleep at night but remains awake during the day.

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation and delirium in adult ICU patients. Crit Care Med 2013;41:263-306.
2. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-82.
3. Colombo R, Corona A, Praga F, et al. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. Minerva Anestesiol 2012;78:1026-33.

and circadian rhythm (also known as *process C*). Process S promotes regulation of both sleep length and depth through melatonin and the neurotransmitter adenosine secretion. Process C controls wakefulness by influencing the timing and duration of the sleep-wake cycle and regulating the hypothalamic central pacemaker. The suprachiasmatic nucleus in the sleep center regulates sleep by controlling melatonin and neurotransmitter release and coordinating the peripheral clocks found in various tissues and organs of the body. These in turn regulate various metabolic, neuroendocrine, and cardiovascular functions (Kamdar 2012). This complex system can be disrupted by many common ICU factors (e.g., critical illness, noise, light, medications, procedures, pain, mechanical ventilation), making altered sleep and circadian dysrhythmias common in critically ill adults (Billings 2015; Pisani 2015).

Sleep physiology varies greatly between healthy and critically ill adults. The normal sleep cycle consists of two phases: non–rapid eye movement (NREM) sleep, which contributes to 75% of total sleep time (TST); and rapid eye movement (REM) sleep, which contributes to 25% of TST. The NREM sleep phases associated with an increasing sleep depth are phase 1 (5% of TST), marked by drowsiness, decreased eye movement, and muscle activity; phase 2 (50% of TST), marked by some awareness and easy arousability with noise; and phase 3 (20% of TST), often called slow-wave sleep (SWS), marked by deep and restful sleep in which restorative functions such as memory consolidation and tissue healing occur. In REM sleep, cerebral and physiologic activity is maximal, and dreaming and perceptual learning are most likely to occur. Four or five sleep cycles of 100 minutes normally occur each night. Any awakening truncates this cycle and results in a return to phase 1 sleep (Kamdar 2012).

Compared with healthy adults, critically ill adults have far more sleep awakenings and thus substantially shorter sleep cycles (Box 1-2). One study of adult ICU patients found that patients had an average of 41 ± 28 sleep cycles every 24 hours, each lasting an average of only 15 ± 9 minutes (Freedman 2001). Critically ill adults therefore spend most of their time in lighter NREM phases 1 and 2 sleep and little time in SWS or REM sleep. Moreover, circadian rhythm abnormalities in this population result in frequent nighttime wakefulness and a sleep pattern in which often half of the TST occurs during the day (Gabor 2003; Freedman 2001).

Box 1-2. Sleep Abnormalities in Critically Ill Patients

- Total sleep time: Unchanged/decreased
- Sleep latency: Unchanged/increased
- Sleep efficiency: Decreased
- NREM stage 1: Increased
- NREM stage 2: Increased
- Sleep fragmentation: Increased
- NREM stage 3: Decreased
- NREM stage 4: Decreased
- REM: Decreased

NREM = non–rapid eye movement; REM = rapid eye movement.
Information from: Friese RS. Sleep and recovery from critical illness and injury: a review of theory, current practice, and future directions. Crit Care Med 2008;36:697-705.

Evaluation of Sleep in the ICU

Patient/Clinician Reported

Critically ill patients commonly report poor sleep as one of their worst memories and an important source of stress and anxiety. Most patients rate sleep quality during their ICU stay as poor or very poor, with memories of insomnia and frequent awakenings commonly reported (Little 2012). The fatigue, fear, anxiety, and physiologic stress associated with sleep deprivation in the ICU makes the recognition of disrupted sleep important. However, clinicians often fail to recognize disrupted sleep in their ICU patients and often overestimate the quality of sleep (Hopper 2015; Kamdar 2012). Although validated sleep quality questionnaires for ICU patients are available (e.g., the Richards-Campbell Sleep Questionnaire), their results often disagree with objective evaluation methods like polysomnography (PSG), their validity in patients with delirium is poor, and they cannot be used in patients requiring deeper sedation (Elliott 2013; Kamdar 2012; Nicolás 2008; Frisk 2003; Richards 2000).

Objective Methods – PSG, Actigraphy, Bispectral Analysis

Polysomnography, considered the gold standard objective measurement of sleep quality and quantity, involves electroencephalographic (EEG), electrooculographic, electromyographic, and ECG evaluations. Polysomnography is the only method that categorizes sleep into both REM and NREM (phases 1–3). However, PSG can be technically challenging to perform in critically ill patients who are uncooperative. Moreover, PSG requires a trained technician to do the assessment and a sleep physician to interpret the results (Bourne 2007). In addition, sedatives, electrical stimuli from other equipment, and commonly encountered ICU medical conditions such as sepsis, encephalopathy, and renal failure can alter EEG reading results (Kamdar 2012; Blume 2006; Kaplan 2004). Although several studies have explored the utility of PSG evaluation in the ICU, variability in the duration and timing of monitoring, a lack of control for the factors that can influence PSG results, and a lack of consensus on how PSG results should be interpreted currently restrict PSG use to the research setting.

Actigraphy is a watch worn on the wrist or ankle that measures patterns of rest and activity. Although it estimates TST, the number and frequency of awakenings, and sleep efficiency, it does not evaluate the stage or quality of sleep. Moreover, actigraphy overestimates sleep compared with PSG, particularly in patients with ICU-acquired weakness or

who are paralyzed or restrained. The role of actigraphy in the ICU therefore remains limited (Pisani 2015; Bourne 2007).

The Bispectral Index (BIS) analysis, a mathematically processed EEG parameter, ranges from 0 (no EEG activity) to 100 ("awake") and can be used to measure depth of sedation during anesthesia. Although reduced BIS scores have been associated with faster sleep onset and an increased depth of sleep in healthy volunteers, BIS cannot characterize the stages of sleep, and several ICU-specific factors (e.g., use of sedation, presence of delirium, and electrical interference from other equipment) preclude its routine use in the ICU for this role (Bourne 2007).

Consequences of Disrupted Sleep

Sleep dysfunction negatively affects normal body homeostasis and has many unwanted neurocognitive, respiratory, immunologic, and metabolic effects. Sleep deprivation increases anxiety, pain, and depression and reduces cognitive function. In addition, it hinders liberation from mechanical ventilation by altering the ventilatory response to hypoxia and hypercarbia and reducing respiratory muscle strength. Sleep disruption activates the sympathetic nervous system, leading to hypertension and tachycardia. With both the humoral and the innate immune systems down-regulated, the risk of infection is greater. Circadian rhythm alterations increase cortisol release and decrease melatonin release, leading to increased catabolic activity and oxygen consumption. Hyperglycemia may also occur, given that sleep disruption may increase insulin resistance and reduce glucose clearance (Billings 2015; Kamdar 2012).

FACTORS THAT DISRUPT SLEEP IN THE ICU

Many common ICU- and critical illness–related factors alter the normal sleep cycle, including excessive noise and light, asynchrony with the mechanical ventilator, patient interruption for care activities, uncontrolled pain, and drugs.

Noise

Excessive noise in the ICU results in frequent awakenings and is a common patient complaint. To prevent sleep disruption, WHO recommends that background noise not exceed 30 dBA and noise interruptions not exceed 45 dBA. However, noise levels in many ICUs often exceed 70 dBA – a noise level associated with heavy city traffic (Darbyshire 2013). Common ICU-specific sources of noise include conversations (from both staff and families), other patients, alarms, nebulizers, telephones, infusion pumps, and equipment (Delaney 2015).

Light

Although critically ill patients do not commonly report light as a direct cause of interrupted sleep, it plays an important role in maintaining circadian pacemaker function. A light intensity of 200–400 lux, equivalent to a regular fluorescent light, suppresses melatonin secretion, a key component of circadian rhythm normalcy (Brezinski 1997).

Patient-Ventilator Interaction

Use of mechanical ventilation alters the sleep cycle (i.e., increase NREM sleep, reduce SWS and REM sleep), increases the frequency of sleep arousals, and causes fragmentation and disruption of the circadian rhythm (Ozsancak 2008; Cooper 2000). Pressure modes of ventilation (e.g., pressure control) are associated with more sleep disruption than volume modes of ventilation (e.g., assist control) because of their greater association with ventilator dyssynchrony (Toublanc 2007; Parthasarathy 2002).

Medications

Many drugs commonly administered to critically ill patients may affect sleep (Table 1-6). Although benzodiazepines and propofol increase TST, decrease time to sleep, reduce arousals, and prolong stage 2 sleep, they reduce REM and SWS time and thus reduce sleep quality (Kondili 2012; Feshchenko 1997; Achermann 1987; Borbély 1985). Benzodiazepines can induce paradoxical effects such as hallucinations, nightmares, and insomnia. Moreover, prolonged use at high doses may induce a withdrawal syndrome that also reduces sleep (Cammarano 1998). Finally, because benzodiazepine use is associated with increased delirium, additional delirium-associated sleep disturbances are likely. Limited non-ICU data show that opioid use may result in sleep dysfunction. However, the critical importance of opioids in treating pain in this population outweighs any concern about worsening sleep (or inducing delirium) and should thus not preclude their use (Dimsdale 2007; Shaw 2005). Although corticosteroids increase REM latency and reduce SWS in healthy patients, their effect on sleep in the critically ill population has not been evaluated (Moser 1996).

Relationship Between Sleep and Delirium

Sleep disruption has been hypothesized to be a risk factor for delirium (Pisani 2015). Cognitive dysfunction may occur during periods of severe sleep deficit; cerebral perfusion and cortical metabolism are altered during both delirium and altered sleep states; and altered circadian rhythmicity may influence the fluctuation of delirium symptoms (Oldman 2016; Pisani 2015). Despite their similarities, our understanding of the pathogenic and functional framework of delirium and sleep deprivation remains limited. The functional alterations of delirium in the brain are unclear; the ability to characterize sleep in the critically ill, even with PSG, is poor; and the neurologic mechanisms that regulate sleep and delirium are intractably linked (Weinhouse 2015; Sanders 2013; Drouot 2012). Investigations into the relationship between sleep disruption and delirium have been small, used non-validated methods to evaluate sleep or diagnose delirium, or failed to control for non-sleep factors that may increase

Table 1-6. Medications That Affect Sleep in the ICU

Pharmacologic Agent or Class	Sleep Abnormalities
Sedatives/hypnotics	
Benzodiazepines	↓ REM, SWS, SL, W ↑ TST
Propofol	↓ SL, W ↑ TST
α_2-Agonists (e.g., dexmedetomidine)	↓ SL, REM ↑ SWS
Analgesics	
Opioids	↓ TST, REM, SWS ↑ W
NSAIDs	↓ TST, SE
Antipsychotics	
Typical antipsychotics (e.g., haloperidol)	↓ W, SL ↑ SE
Atypical antipsychotics (e.g., olanzapine)	↓ W, SL ↑ TST, SE, SWS
Antidepressants	
Tricyclic antidepressants	↓ W, REM ↑ TST
SSRIs	↓ REM, TST, SE ↑ W
Trazodone	↓ W, SL, REM ↑ TST ± SWS
Cardiovascular	
α_2-Agonists	↓ REM
β-Antagonists	↑ W, SL ↓ REM Note: Alterations are more likely to occur with agents that are lipid soluble
Calcium antagonists	N/A
ACE inhibitors	No effect on sleep
Diuretics	N/A
Amiodarone	Nightmares

Table 1-6. (*Continued*)

Vasopressors	
Dopamine	↓ REM, SWS
Norepinephrine/epinephrine	↓ REM, SWS
Respiratory	
Xanthines (e.g., theophylline)	↓ SWS, TST, SE, REM ↑ W
Anticonvulsants	
Phenytoin	↓ SL ↑ SWS
Phenobarbital	↓ W, SL, REM ↑ TST
Carbamazepine	↓ REM, SL ↑ SWS
Valproic acid	↓ W ↑ TST
Gabapentin	↓ W ↑ TST, REM, SWS
Corticosteroids	
Methylprednisolone, hydrocortisone	↓ REM, SWS ↑ W

ACE = angiotensin-converting enzyme; N/A = not applicable; REM = rapid eye movement; SE = sleep efficiency; SL = sleep latency; SSRI = selective serotonin reuptake inhibitor; SWS = slow-wave sleep; TST = total sleep time; W = wakefulness.

Information from: Bourne RS, Mills GH. Sleep disturbances in critically ill patients – pharmacology considerations. Anaesthesia 2004;59:374-84; and Weinhouse GL. Pharmacology I: effects on sleep of commonly used ICU medications. Crit Care Clin 2008;24:477-91.

delirium (Weinhouse 2014). One study using 24-hour PSG evaluation failed to show a relationship between delirium occurrence and sleep patterns (Boesen 2016). Further studies are needed to evaluate the relationship between sleep and delirium in the ICU.

INTERVENTIONS TO IMPROVE SLEEP IN THE ICU

Nonpharmacologic

Earplugs/Music

Applying earplugs at night in the ICU is associated with reduced delirium but has not been shown to improve sleep. Patients in earplug or noise-canceling headphone studies have generally been awake and able to self-report pain and anxiety; little evidence supports earplug use in patients who are sicker or who require deeper levels of sedation (Litton 2016; Hu 2015). Some ICU patients may not like having earplugs placed, and without reminders, nurses may forget to take them out, leading to prolonged periods in which patients are more disconnected from their environment and thus more susceptible to delirium. Adding music to noise-canceling strategies like earplugs may increase benefits. In one large, multicenter, randomized study of mechanically ventilated, critically ill adults, music therapy administered by noise-canceling headphones reduced patient anxiety and sedative use more than noise-canceling headphones without music (Chlan 2013).

Environmental Modification

Although reducing noise in the ICU is a low-risk strategy that should always be considered, evidence that specific strategies improve patient outcome is mixed (Tainter 2016; Patel 2014a; Kamdar 2013). Light in the ICU can negatively affect the sleep-wake cycle and may increase delirium; therefore,

efforts to reduce nocturnal light should be considered (Elliott 2013; Little 2012). Although no studies examined the impact of only light reduction interventions on sleep in critically ill patients, several studies evaluated a combined noise and light reduction bundle, finding mixed effects on delirium occurrence and sleep quality (Patel 2014a; Kamdar 2013; Li 2011).

Common patient care activities (e.g., baths, breathing treatments, medication administration), mechanical interventions (e.g., dressing changes, intravenous line maintenance, endotracheal suctioning, oral hygiene), and physical assessments (e.g., blood glucose, vital signs, neurologic checks, equipment monitoring) can also lead to sleep disruptions. Critically ill patients are often awakened at night because of patient care activities and often kept awake for varying durations (Tamburi 2004; Gabor 2003). Clustering of patient care activities and removal of unnecessary interventions improve sleep quality and should be considered (Li 2011).

Ventilator Adjustment

Resting patients at night on a volume mode of ventilation (i.e., assist control) decreases sleep fragmentation, reduces central apnea and hyperventilation, and promotes reduced wakefulness and increased NREM sleep (Toublanc 2007; Parthasarathy 2002). Use of nocturnal proportional assist ventilation (compared with a pressure support mode) results in improved sleep quality and decreased ventilator dyssynchrony (Bosma 2007). Therefore, use of a nocturnal assist control ventilation mode should be considered in intubated patients who cannot sleep.

Pharmacotherapy

Nonbenzodiazepine Sedatives

Data on the relationship between dexmedetomidine and sleep are limited but promising. In several studies, sedation with dexmedetomidine produced EEG-BIS patterns that mimic NREM sleep in contrast to GABA agonists such as benzodiazepines and propofol (Huupponen 2008; Coull 2004). Studies evaluating dexmedetomidine's effect on sleep structure have been small and mostly uncontrolled and produced mixed results. In one study, patients who received nocturnal dexmedetomidine had preservation of day-night sleep cycle, with most TST occurring at night, and enhanced NREM phases 1 and 2 sleep, but not SWS or REM sleep (Oto 2012). In another study, patients who received nocturnal dexmedetomidine had similar findings with TST, NREM phase 2 sleep, REM, and SWS, but they had less NREM phase 1 sleep during the infusion (Alexopoulou 2014). Additional large controlled studies that account for the many factors that can disrupt sleep in the ICU are needed to further evaluate the role of dexmedetomidine in sleep quality and delirium.

Zolpidem is a non-benzodiazepine derivative that binds to the type 1 benzodiazepine receptor subtype and increases TST. In non-critically ill patients, latency to REM is increased, but time spent in REM may not be affected (Merlotti 1989). However, the role of zolpidem in sleep in critically ill patients has not been evaluated, and its anticholinergic properties may increase the risk of delirium. Therefore, zolpidem cannot be recommended for critically ill patients at this time.

Melatonin/Melatonin Analogs

Five placebo-controlled trials have evaluated the role of melatonin agonists in the critically ill population; all studies varied considerably in methodology and dosing regimens (Table 1-7). No difference was found between the two studies evaluating sleep quality (Bourne 2008; Shilo 2000). Rates of delirium were lower in patients administered a melatonin analog in the one study that evaluated it (Hatta 2014). Despite the lack of robust data and the need for larger controlled studies, melatonin agonists may be an option for treating sleep disruption in the ICU because of their ease of use and favorable adverse effect profile.

Antidepressants

Antidepressants with sedating properties are commonly used for sleep dysfunction because of their ability to decrease sleep latency and arousals and increase TST. However, their effects on REM and SWS are limited (Weinhouse 2008). Antidepressants have not been studied for sleep disorders in the ICU, and some, in fact, may increase the risk of delirium because of their anticholinergic and serotonergic properties. Therefore, their use for this indication cannot be recommended at this time.

Antipsychotics

Antipsychotics are increasingly used to manage delirium in critically ill patients. Although no published studies have directly evaluated this relationship in critically ill patients, several small studies of largely healthy volunteers suggest that antipsychotics positively affect sleep (Weinhouse 2008).

Olanzapine increases TST and SWS, but its effect on sleep efficiency, other NREM sleep stages, and REM sleep remains unclear (Giménez 2007; Lindberg 2002; Sharpley 2000). Quetiapine at higher doses was associated with increased leg movement and improved TST, sleep efficiency, NREM phase 2 sleep, subjective sleep quality, and sleep time (Cohrs 2004). Haloperidol improved sleep efficiency and NREM phase 2 sleep, with small effect on SWS or REM compared with placebo, although the results were not statistically significant, likely because of the small sample size (Giménez 2007). Increased TST, sleep efficiency, and NREM phase 3 sleep have occurred with risperidone (Yoshimura 2007). Further studies, particularly of critically ill patients, are needed before antipsychotics can routinely be recommended for sleep disorders in the ICU.

CONCLUSION

Both delirium and sleep disruption are common in critically ill patients. A causal relationship between the two has not been fully elucidated, but existing data support that they

Table 1-7. Melatonin Agonists for Sleep Management in the ICU

Author (year)	Patient Population	Intervention and Control	Measurement of Sleep	Delirium Measured	Sleep Quality (melatonin vs. placebo, where applicable)	Sedation Results (melatonin vs. placebo, where applicable)
Shilo (2000)	Medical: 100%; mechanical ventilation: 29%	**Pharmacologic:** Day 1: pre-intervention Days 2 + 3: Melatonin 3 mg daily at 10 p.m. (n=8) **Nonpharmacologic:** Nocturnal light dimming and noise reduction **Control:** Placebo (n=6)	Actigraphy	NR	TST: 6.3 ± 1.1 hr vs. 7.4 ± 2.1 hr; p=NR Awakenings: 1.4 ± 3.7 vs. 1.8 ± 6.3; p=NS	NR
Ibrahim (2006)	NR; mechanical ventilation: 100%	**Pharmacologic:** Melatonin 3 mg daily at 10 p.m. for at least 48 hr or until ICU discharge (n=14) **Nonpharmacologic:** NR **Control:** Placebo (n=18)	Duration subjectively observed by nurses without formal measurement	NR	Duration of nocturnal sleep, diurnal sleep; p=NS	Haloperidol for agitation; p=NS
Bourne (2008)	Medical: 88%; mechanical ventilation: 100%	**Pharmacologic:** Melatonin 10 mg daily at 9 p.m. for 4 days (n=12) **Nonpharmacologic:** Earplugs and eye masks at patients' discretion, minimize nocturnal noise and clinical disturbances **Control:** Placebo (n=12)	BIS Actigraphy RCSQ	NR	BIS SEI difference: 0.12; p=NS BIS AUR difference: -54.2; p=0.04 Actigraphy: 0.7 (0.5–0.9) vs. 0.8 (0.7–0.8); p=NS RCSQ: 0.4 (0.2–0.6) vs. 0.5 (0.4–0.6); p=NS	Haloperidol for agitation; p=NS
Hatta (2014)	Medical: 100%; mechanical ventilation: 0%	**Pharmacologic:** Ramelteon 8 mg daily at 9 p.m. for 7 days (n=33) **Nonpharmacologic:** Mobilization, adequate light, noise reduction, clocks, calendars, regular communication **Control:** Placebo (n=34)	Difficulty falling and staying asleep, awakenings, poor sleep quality, duration measured with patient and nurse reporting	3% vs. 32%; p=0.003	Difficulty falling and staying asleep, awakenings, poor sleep quality, duration of sleep; p=NS	Hydroxyzine for insomnia; p=NS
Mistraletti (2015)	Medical: 63%; mechanical ventilation: 87%	**Pharmacologic:** Days 1 + 2: pre-intervention Day 3: melatonin 3 mg daily at 8 p.m. and midnight (n=41) until ICU discharge/death/study suspension **Nonpharmacologic:** NR Control: Placebo (n=41)	Duration subjectively observed by nurses without formal measurement	NR	NR	Hydroxyzine for sedation (mg/kg/vent day): 0.6 (0–2.4) vs. 3 (0.2–3.8); p=0.01

Data are presented as median (interquartile range); AUR = area under the curve; NS = nonsignificant; NR = not reported; RCSQ = Richards-Campbell Sleep Questionnaire; SEI = sleep efficiency index.

Information from: Shilo L, Dagan Y, Smorjik Y, et al. Effect of melatonin on sleep quality of COPD intensive care patients: a pilot study. Chronobiol Int 2000;17:71-6; Ibrahim MG, Bellomo R, Hart GK, et al. A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients. Crit Care Resusc 2006;8:187-91; Bourne RS, Mills GH, Minelli C. Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. Crit Care 2008;12:R52; Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium. JAMA Psychiatry 2014;71:397-403; and Mistraletti G, Umbrello M, Sabbatini G, et al. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. Minerva Anestesiol 2015;81:1298-310.

may be related. Clinicians must be aware of strategies to mitigate the risk of delirium and sleep disruption, including reversal of modifiable risk factors, as appropriate; the use of validated and feasible screening tools; and development of evidence-based plans that prioritize nonpharmacologic interventions.

A multidisciplinary, bundled approach (e.g., the ABCDEF bundle) should be used to recognize and reduce delirium in critically ill patients. This requires that a member of the ICU team evaluate all patients for delirium at least once per shift and that the results of these evaluations be documented in the patient record. At least daily during patient care rounds, the ICU team should discuss the results of delirium assessments, strategies to reduce potential modifiable ICU delirium risk factors, and the use of nonpharmacologic strategies to reduce delirium incidence and associated burden.

A protocolized, integrated management approach that includes pain assessment (in addition to sedation and delirium), automatic sedation-minimizing strategies (e.g., daily interruption), and an early mobilization strategy significantly improves patient outcomes by reducing the duration of mechanical ventilation and ICU length of stay; avoiding the complications associated with inadequate or inappropriate management of pain, agitation, and delirium; and decreasing health care costs.

Clinicians should evaluate the patients under their care and identify those for whom an opportunity to improve sleep is present. Such patients are often recovering from critical illness and do not require continuous sedation. A protocolized sleep bundle that incorporates pharmacologic and nonpharmacologic prevention and treatment strategies, particularly eye masks and earplugs, should be developed and used in patients with evidence of disrupted sleep.

Practice Points

Delirium Outcomes

- Delirium is associated with increased ICU, hospital, and longer-term mortality.
- Delirium is associated with prolonged ICU and hospital lengths of stay.
- Delirium is associated with the development of post-ICU cognitive impairment.

Detecting and Monitoring Delirium

- Routine delirium monitoring should be performed, preferably at least twice daily.
- The CAM-ICU and ICDSC are the most valid and reliable ICU delirium monitoring tools.
- Interdisciplinary monitoring of delirium is feasible and sustainable in ICU clinical practice.

Delirium Risk Factors

- Four baseline risk factors are significantly associated with the development of delirium in the ICU: preexisting dementia, history of hypertension, history of chronic alcohol use, and high severity of illness at the time of admission.
- Sedation-induced coma is a risk factor for delirium and should be avoided.
- Sedatives should be considered, and at the lowest effective dose, only after pain has been evaluated and treated and nonpharmacologic strategies to calm patients have failed.
- The relationship between opioid use and delirium remains unclear; opioids should not be avoided in a patient who has pain.
- Benzodiazepines are an important risk factor for delirium, and their use should be avoided unless a compelling indication exists (e.g., acute seizure; benzodiazepine withdrawal).
- The relationship between propofol and delirium remains unclear.

Delirium Prevention

- Early mobilization, frequent orientation, and strategies to improve sleep (e.g., earplugs) should be considered.
- A pharmacologic delirium prevention protocol in adult critically ill patients cannot be recommended because no compelling data show that this reduces the incidence or duration of delirium in these patients.
- Haloperidol or atypical antipsychotics should not be administered to prevent delirium in the ICU.
- No recommendations can be made regarding the use of dexmedetomidine for the prevention delirium in adult critically ill patients because there is no compelling evidence regarding its effectiveness in these patients.

Delirium Treatment

- Haloperidol has never been shown in a randomized trial to reduce delirium but may play a role in reducing delirium symptoms that are bothersome to patients (e.g., hallucinations) or in managing severe agitation that is unrelated to pain or medication withdrawal.
- Evidence supporting the use of atypical antipsychotics remains weak. One small controlled study evaluating quetiapine suggests that delirium resolves faster with its use.
- Rivastigmine should not be used to reduce delirium because it is associated with higher mortality.
- Antipsychotics should be avoided in patients at risk of torsades de pointes (e.g., patients with baseline prolongation of QTc interval, patients receiving concomitant medications known to prolong the QTc interval, or patients with a history of torsades de pointes).
- Dexmedetomidine should be considered, rather than a benzodiazepine, for patients with delirium who have severe agitation that is believed to be unrelated to pain or benzodiazepine withdrawal. The role of dexmedetomidine as adjunct therapy for managing alcohol withdrawal, a condition that should be managed differently from agitated delirium, is emerging.

Sleep Disruption

- Increased awakenings and shortened sleep cycles are common. NREM phase 1 and 2 sleep increases; SWS or REM sleep is decreased and often nonexistent.
- Daytime sleep is prevalent because of circadian rhythm abnormalities.

Practice Points (continued)

Sleep Evaluation

- **Disrupted sleep is often unrecognized, and sleep quality is often overestimated. Sleep quality should be evaluated, when possible, using questionnaires or more objective means.**
- **PSG remains the gold standard method to evaluate sleep in the ICU, but its routine use is limited because of technical challenges, including the need for a trained technician and evaluator and the many critical illness–related factors that affect its precision.**
- **Actinography has a limited role because it evaluates neither the stage nor the quality of sleep, and several critical illness–related factors affect reported results.**

Factors That Disrupt Sleep

- **Noise and light levels in the ICU are often high and disrupt sleep.**
- **Mechanical ventilation, particularly when a pressure mode is used, reduces sleep quality and increases sleep arousals and fragmentation.**
- **Several medications may negatively alter sleep.**
- **The relationship between sleep and delirium remains unclear, but interventions focused on reducing sleep disruptions reduce delirium.**

Interventions to Improve Sleep

- **Nocturnal nonpharmacologic therapy, including earplugs, music, eye masks, environmental noise and light reduction, and bundling of patient care activities, should be considered.**
- **Nocturnal assist control ventilation mode should be considered in intubated patients who have difficulty sleeping.**
- **The role of dexmedetomidine as a strategy to promote sleep quality requires further study. In a patient with agitation unrelated to pain who has complaints of interrupted sleep, it can be considered if the patient cannot receive antipsychotic therapy (e.g., QTc prolongation, lack of enteral access, or contraindication to enteral administration).**
- **Sedation, particularly with benzodiazepines, should be minimized because they are a proven cause for delirium, and there is a proven association between delirium and disrupted sleep.**
- **Zolpidem and sedating antidepressants are not recommended.**
- **The evidence for using a melatonin analog or an antipsychotic to improve sleep remains weak. However, they may be considered in patients with complaints of poor-quality sleep. Antipsychotics should only be considered in patients who do not have QTc prolongation.**
- **Protocols that outline pharmacologic and nonpharmacologic strategies to improve sleep are recommended.**

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

M.J. is a 67-year-old man with a history of chronic constipation. He is given a diagnosis of colonic perforation. On admission, his temperature is 38.5°C, blood pressure is 80/60 mm Hg, heart rate is 105 beats/minute, and SaO_2 is 90% on room air. After intubation, resuscitation, and administration of empiric piperacillin/tazobactam, M.J. undergoes a subtotal colectomy. He is transferred to the surgical ICU on postoperative day (POD) 0 intubated and receiving several intravenous infusions, including propofol 40 mcg/kg/minute, fentanyl 75 mcg/hour, norepinephrine 20 mcg/minute, and vasopressin 0.04 unit/minute. His Richmond Agitation-Sedation Scale (RASS) score is -4.

1. After M.J.'s propofol is decreased to 20 mcg/kg/minute, his RASS increases to +2, and his Critical-Care Pain Observation Tool (CPOT) score is 2, indicating no pain. However, M.J. does not recognize his wife at his bedside. He tries to self-extubate and pull out his nasogastric tube, despite encouragement from his nurse to calm down. His nurse does a Confusion Assessment Method for the ICU (CAM-ICU) evaluation and determines that M.J. fails the "SAVE A HAART" assessment. Given these CAM-ICU results and M.J.'s current clinical status, which one of the following best describes M.J.'s cognitive status?

   A. He does not have delirium because his current level of agitation precludes the CAM-ICU.
   B. He has delirium because he has inattention and altered level of consciousness.
   C. He does not have delirium because his nurse did not evaluate him for disorganized thinking.
   D. He has delirium because he has an acute change in mental status, inattention, and altered level of consciousness.

2. Shortly after M.J.'s CAM-ICU evaluation by the nurses, a psychiatrist arrives. He evaluates M.J. and determines that he has delirium. Which one of the following best characterizes M.J.'s delirium at this time?

   A. Hypoactive
   B. Hyperactive
   C. Mixed
   D. Subsyndromal

3. On day 3 of his surgical ICU stay, M.J. is still receiving both propofol and fentanyl infusions. His RASS is -3, and the nurse deems that he is not a candidate for a spontaneous awakening trial (SAT). A CAM-ICU evaluation at this time is positive. Which one of the following best summarizes M.J.'s delirium assessment and diagnosis?

   A. The Intensive Care Delirium Screening Checklist (ICDSC), rather than the CAM-ICU, should have been used.
   B. The CAM-ICU screening results are not valid because the patient is too sedated.
   C. His level of sedation has no influence on whether a CAM-ICU assessment will be positive.
   D. He may have rapidly reversible delirium because a SAT was not performed before the CAM-ICU assessment.

4. M.J. is eventually discharged from the ICU to a general surgery ward but remains in delirium. His persistent, fluctuating agitation (that is not related to pain) requires the presence of a sitter. Which one of the following outcomes is M.J. most likely to have?

   A. Transfer from the surgical ward to a rehabilitation facility
   B. Transfer from the surgical ward to a nursing home
   C. Ability to return to playing bridge with his friends in 2 months
   D. Risk of dying at 6 months similar to a surgical ICU patient who did not develop delirium

Questions 5–8 pertain to the following case.

N.P., a 32-year-old man who lives alone, fell from the third floor of his apartment building. He presents to the ED with several rib fractures, a hip fracture, and a pneumothorax. N.P. is intubated, a chest tube is placed, and he undergoes an open reduction and internal fixation of his right hip in the operating room. On POD 1, N.P. remains in the surgical ICU. He is receiving propofol 50 mcg/kg/minute and fentanyl 100 mcg/hour, and he is restrained. His RASS is -1, and his CPOT is 2, indicating no pain.

5. Which one of the following best describes N.P.'s strong risk factors for delirium?

   A. Mechanical ventilation, restraint use, and trauma requiring operating room stabilization
   B. Mechanical ventilation, restraint use, and coma
   C. Mechanical ventilation, living alone, and fentanyl use
   D. Mechanical ventilation, trauma requiring operating room stabilization, and propofol use

6. On the morning of POD 3, N.P.'s propofol infusion is discontinued. Because of a CPOT of 4, indicating pain, his fentanyl infusion is increased from 200 mcg/hour to 300 mcg/hour. His most recent RASS is -1. Late in the afternoon, N.P. is increasingly hypotensive, and his Hgb concentration is 5.8 mg/dL. His ICDSC score is 5. After being administered

4 units of packed red blood cells, N.P. is taken for an abdominal CT scan, which reveals a retroperitoneal bleed. On the way back from the CT suite, he becomes increasingly agitated and is administered lorazepam 5 mg intravenously once. A full body rash appears, and he is initiated on diphenhydramine 50 mg intravenously every 6 hours and methylprednisolone 40 mg intravenously every 12 hours. Over the next 24 hours, while his bleeding stabilizes, N.P.'s level of agitation increases, and he is initiated on a lorazepam infusion at 5 mg/hour. Which one of the following is most likely potentiating N.P.'s delirium?

A. Diphenhydramine
B. Lorazepam
C. Methylprednisolone
D. Fentanyl

7. Which strategy would most likely decrease the duration of delirium in N.P.?

A. Ensure family members are regularly at his bedside.
B. Insert earplugs at night.
C. Play his favorite music in the background.
D. Maximize early mobilization efforts.

8. Which one of the following pharmacologic strategies is best to recommend for managing N.P.'s increased agitation while considering his delirium?

A. Substitute dexmedetomidine for lorazepam.
B. Substitute midazolam for lorazepam.
C. Initiate scheduled quetiapine therapy.
D. Initiate scheduled haloperidol therapy.

Questions 9–13 pertain to the following case.

M.L. is a 79-year-old woman admitted to the medical ICU for severe acute respiratory distress syndrome caused by worsening community-acquired pneumonia. On ICU day 5, she is mechanically ventilated on maximal ventilatory support. She currently receives infusions of midazolam 4 mg/hour, fentanyl 250 mcg/hour, and cisatracurium 2 mcg/kg/minute. M.L. is at her RASS goal of -5. Her laboratory values show hyponatremia (current 125 mEq/L, baseline 135 mEq/L), acute renal failure (current SCr 2.5 mg/dL, baseline SCr 0.7 mg/dL), and a rising lactate (most recently 4 mmol/L). M.L.'s other laboratory values are within normal limits.

9. Which one of the following would best reduce M.L.'s risk of delirium?

A. Manage her hyponatremia with 0.9% sodium chloride infusion.
B. Replace midazolam with dexmedetomidine.
C. Administer melatonin nightly.
D. Replace fentanyl with hydromorphone.

10. By day 7, M.L.'s oxygenation improves and she is placed on a pressure support mode of mechanical ventilation. The cisatracurium infusion has been discontinued. The medical team decides to continue midazolam 4 mg/hour and fentanyl 150 mcg/hour. M.L. is tolerating enteral nutrition by feeding tube (FT) at 40 mL/hour. During a 2-hour SAT, she becomes severely agitated (RASS +4), requiring resumption of the earlier infusions. During the SAT, her ICDSC is 6, and her CPOT is 2. Which one of the following is the most appropriate intervention to consider in M.L., given the SAT?

A. Reinitiate fentanyl at 75 mcg/hour, and convert to lorazepam 4 mg every 6 hours by FT with midazolam 2 mg intravenously every 4 hours as needed for agitation.
B. Reinitiate fentanyl and midazolam infusions at the same pre-SAT dose.
C. Reinitiate fentanyl and midazolam infusions at the same pre-SAT dose; add quetiapine 50 mg by FT every 12 hours.
D. Reduce the fentanyl infusion to 75 mcg/hour; initiate lorazepam 4 mg every 6 hours by FT and dexmedetomidine 0.2 mcg/kg/hour titrated to maintain a RASS of -1.

11. On ICU day 9, M.L.'s ICDSC is 5. She has been weaned off all intravenous infusions and is currently receiving lorazepam 1 mg every 6 hours by FT and hydromorphone intravenously every 6 hours as needed for pain. M.L. consistently has RASS scores of +1 to +3. Her pain is 3 using the numeric rating scale (NRS), indicating mild pain. Her QTc interval is 430 milliseconds. The ICU team wants to initiate treatment for agitated delirium. Which one of the following is best to recommend for M.L.?

A. Quetiapine 50 mg twice daily by FT
B. Rivastigmine 1.5 mg twice daily by FT
C. Melatonin 10 mg at bedtime by FT
D. Haloperidol 1 mg/hour continuous infusion

12. On ICU day 13, M.L. is ICDSC delirium positive for hypoactive delirium and her RASS is -1. She is initiated on a dexmedetomidine infusion to maintain a RASS of -2. Which one of the following is best to recommend regarding the use of dexmedetomidine in M.L.?

A. Continue dexmedetomidine until she becomes CAM-ICU negative.
B. Discontinue dexmedetomidine and optimize nonpharmacologic delirium prevention/treatment interventions.
C. Continue dexmedetomidine and optimize nonpharmacologic delirium prevention/treatment interventions.
D. Discontinue dexmedetomidine and initiate intermittent intravenous diphenhydramine to reach sedation goal.

13. On ICU day 13, M.L. is vomiting and given a diagnosis of ileus. She develops atrial fibrillation, for which she is given intravenous amiodarone. M.L.'s most recent ECG reveals a QTc interval of 520 milliseconds, and her heart rate is 49 beats/minute. Her enteral feeds and the drugs currently administered by FT are held. She then becomes acutely agitated (RASS +3). Her ICDSC is 6. Which one of the following would best manage M.L.'s agitated delirium?

    A. Ziprasidone 10 mg intramuscularly every 12 hours
    B. Haloperidol 5 mg intravenously every 6 hours
    C. Dexmedetomidine 0.2 mcg/kg/hour titrated to a RASS 0 to -1
    D. Valproic acid 750 mg intravenously x 1, followed by 50 mg intravenously every 6 hours

Questions 14–16 pertain to the following case.

K.P. is a 70-year-old man who is admitted to the cardiac ICU (an older unit that has bays rather than rooms) after having an ST-segment elevation myocardial infarction. He has both a Foley catheter and a central line in place and is receiving 2 L of oxygen by nasal prongs. At home, K.P. uses bilevel positive airway pressure (BIPAP) at night for obstructive sleep apnea and occasionally takes quetiapine 50 mg at night to help fall asleep. He is being evaluated for coronary artery bypass grafting. K.P. has no pain or discomfort, and his mental status is at baseline.

14. K.P. reports awakening during the night (but not having trouble falling asleep). Which one of the following tools would best evaluate K.P.'s sleep quality?

    A. RASS
    B. Bispectral Index
    C. Actigraphy
    D. Richards-Campbell Sleep Questionnaire

15. Which one of the following factors is most affecting the sleep quality that K.P. describes?

    A. Failure to reinitiate his home quetiapine and the current use of a Foley catheter
    B. Failure to initiate earplugs and use of home BIPAP at night
    C. Failure to administer lorazepam and initiate earplugs at night
    D. Failure to reinitiate his home quetiapine and the current use of a central line

16. The next night at 9 p.m., K.P.'s temperature is 38.5°C; he has developed a leukocytosis to 16,000 cells/mm^3 and appears confused and agitated (RASS +3). Blood and urine cultures are obtained, and he is initiated on empiric levofloxacin therapy. An ECG obtained in the morning shows a QTc interval of 520 milliseconds. A CAM-ICU evaluation is positive. K.P. tries to remove his Foley catheter and central line, so the nurse fastens restraints on his wrists. The ICU fellow asks your opinion on how to help K.P. sleep. Which one of the following is best to recommend for K.P.?

    A. No pharmacologic intervention is required. His agitation/delirium will resolve once antibiotic therapy is initiated for his infection.
    B. Give quetiapine 50 mg once now.
    C. Give melatonin 3 mg once now.
    D. Initiate dexmedetomidine 0.2 mcg/kg/hour and titrate the infusion to a RASS -1.

Questions 17–19 pertain to the following case.

P.D. is a 39-year-old woman who presents to the ED with several gunshot wounds to the abdomen. She is rushed to the operating room, where she undergoes a partial hepatectomy, small bowel resection, and splenectomy. She presents to the surgical ICU intubated and receiving infusions of propofol 45 mcg/kg/minute, fentanyl 75 mcg/hour, norepinephrine 20 mcg/minute, and vasopressin 0.04 unit/minute. On POD 2, aggressive diuresis and both ventilator and sedation weaning occurs. On POD 3, P.D. is receiving propofol 10 mcg/kg/minute and fentanyl 50 mcg/hour, and she is taken off vasoactive agents. Her RASS is -1, and her pain score (using the NRS) ranges from 0 to 2, indicating no-mild pain. P.D. is currently receiving a pressure support mode of ventilation.

17. On the afternoon of POD 3, P.D. is off all sedation and receiving hydromorphone boluses for pain. At the end of her 3-hour pressure support trial at 10 p.m., P.D. is awake with complaints of difficulty sleeping. Which one of the following interventions may best improve P.D.'s sleep?

    A. Increase the dose of her hydromorphone regimen, and maintain her on a pressure support mode throughout the night.
    B. Initiate dexmedetomidine, place her back on assist control ventilation for 7 hours, and initiate another pressure support trial at 8 a.m.
    C. Place her back on assist control ventilation for 7 hours, and begin another pressure support trial at 8 a.m.
    D. Initiate melatonin, place her back on assist control ventilation for 7 hours, and initiate another pressure support trial at 8 a.m.

18. On POD 6, P.D. is extubated. After extubation, she has increased difficulty sleeping. Which one of the following is best to recommend to improve P.D.'s sleep?

    A. Reduce noise with earplugs, reduce light with an eye mask, and consolidate procedures at night.
    B. Reduce noise with earplugs and light with an eye mask at night.
    C. Reduce noise with earplugs at night.
    D. Eliminate light at night and keep lights on during the day.

19. P.D. seems to have benefited from nonpharmacologic interventions to improve her sleep, but she still has difficulty sleeping at night on POD 8. She remains extubated and is awake and alert, free of pain, and ready for transfer to a surgical non-ICU floor. The ICU fellow approaches you for help. Which one of the following is best to recommend for promoting sleep in P.D.?

    A. Give clonazepam 1 mg once at 9 p.m.
    B. Initiate dexmedetomidine 0.2 mcg/kg/hour now, increase the dose to 0.4 mcg/kg/hour at 9 p.m., and then reduce the dose to 0.2 mcg/kg/hour at 7 a.m.
    C. Give melatonin 3 mg once at 9 p.m.
    D. Give trazodone 50 mg once at 9 p.m.

20. A 66-year-old woman is POD 4 from an aortic valve replacement. Her current problems include cardiogenic shock, for which she is receiving dobutamine and norepinephrine; postoperative atrial fibrillation, for which she is receiving amiodarone; and a UTI, for which she is receiving levofloxacin. Her heart rate is 85 beats/minute, with blood pressure 120/80 mm Hg, QTc interval 521 milliseconds, and temperature 37.5°C. She has difficulty sleeping, despite using earplugs and an eye mask for the past 2 nights. Which one of the following, given once at 9 p.m., is best to recommend for this patient?

    A. Zolpidem 5 mg
    B. Quetiapine 50 mg
    C. Trazodone 50 mg
    D. Melatonin 3 mg

Learner Chapter Evaluation: Delirium and Sleep In Critically Ill Adults.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Demonstrate an understanding of the symptoms, epidemiology, and outcomes of delirium in critically ill adults.
13. Evaluate a critically ill adult for delirium by identifying modifiable risk factors and using a validated screening tool.
14. Design an evidence-based strategy to reduce the burden of delirium in critically ill adults.
15. Apply epidemiology and tools to evaluate sleep disruption in critically ill adults.
16. Detect modifiable factors associated with sleep disruption in critically ill adults.
17. Construct an evidence-based protocol to improve sleep quality and prevent delirium in critically ill adults.
18. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Pain, Agitation, and Delirium Monitoring/Pathway Development

By Joanna L. Stollings, Pharm.D., FCCM, BCPS, BCCCP

Reviewed by John Papadopoulos, Pharm.D., FCCM, BCNSP, BCCCP; and Hesham Mourad, Pharm.D., BCPS, BCCCP

LEARNING OBJECTIVES

1. Apply the different pain monitoring tools used in critically ill patients.
2. Demonstrate how to use the RASS and SAS for monitoring a patient's level of consciousness.
3. Apply validated tools for monitoring delirium.
4. Evaluate the benefits and the components of the ABCDEF bundle in critically ill patients.
5. Justify the role of the interprofessional team, including the pharmacist, in implementing the ABCDEF bundle.

ABBREVIATIONS IN THIS CHAPTER

CAM-ICU	Confusion assessment method for the ICU
CPOT	Critical-Care Pain Observation Tool
ICDSC	Intensive Care Delirium Screening Checklist
PAD	Pain, agitation, and delirium
RASS	Richmond Agitation-Sedation Scale
SAS	Sedation-Agitation Scale
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine

Table of other common abbreviations.

INTRODUCTION

Many critically ill patients experience pain, agitation, and delirium (PAD) during their acute illness. The 2013 Society of Critical Care Medicine (SCCM) PAD guidelines outline the best evidence available for providing physical and psychological comfort through the management of PAD (Barr 2013a). The ability to accurately assess a patient's level of pain is key to effective pain treatment. Using a valid and reliable sedation tool allows the measurement of quality and depth of sedation. Delirium that is not assessed with a validated tool often goes unrecognized. A six-step approach called the ABCDEF bundle includes interventions to decrease sedation exposure, duration of mechanical ventilation, and ICU-acquired delirium and weakness.

PAIN MONITORING

The PAD guidelines recommend that all adult ICU patients be assessed routinely for pain with an objective, valid, and reliable tool. Self-reporting is the gold standard for assessing pain. However, self-reporting is often impossible for patients on mechanical ventilation or receiving psychoactive drugs (Barr 2013b). Pain assessment has been associated with reduced analgesic use, ICU length of stay, and duration of mechanical ventilation (Payen 2009; Payen 2007). The SCCM guidelines committee performed a thorough psychometric analysis of the following pain scales: Behavioral Pain Scale (BPS), BPS-Non Intubated (BPS-NI), Critical-Care Pain Observation Tool (CPOT), Adult Nonverbal Pain Scale (NVPS) (initial and revised NVPS-I and NVPS-R), Pain

Behavior Assessment Tool (PBAT), and Pain Assessment and Intervention Notation (PAIN) algorithm. Both the BPS and CPOT received moderate psychometric scores according to interrater reliability, discriminant validity, and criterion validity in medical, surgical, and trauma patients and thus were recommended by the PAD guidelines for assessing pain in nonverbal ICU patients (Barr 2013a).

The BPS score (Table 2-1) summarizes the three behavioral domains that are scored 1–4 (facial expression, movement of upper limbs, and compliance with mechanical ventilation) for a total possible score of 3–12. A score greater than 5 in nonverbal ICU adult patients is predictive of significant pain (Gelinas 2013). The BPS was originally validated in a prospective study of 30 mechanically ventilated patients receiving analgesia and sedation over a 6-month period in a 10-bed trauma and postoperative ICU. Assessments of the BPS were collected consecutively at standardized times before and during care procedures (Payen 2001). The BPS has been tested in over 500 medical, surgical, and trauma patients. Although the BPS was originally developed in French, it has been translated into English and Chinese. Implementing the BPS has resulted in more pain assessments and improved patient outcomes, including decreased duration of mechanical ventilation and reduced nosocomial infections. The biggest limitations of the BPS are the subjectiveness of interpreting data such as the movement of upper limbs interpreted as muscle rigidity and the lack of a clear definition for compliance with mechanical ventilation (Gelinas 2013).

The CPOT (Table 2-2) is a summation of four different behavioral domains that are given a score of 0–2 (facial expressions, body movements, muscle tension, and compliance with the ventilator for mechanically ventilated patients or vocalization for nonintubated patients) for a score of 0–8. Scores greater than 2 in nonverbal ICU adult patients are predictive of significant pain (Gelinas 2013). The CPOT was originally validated in 103 cardiac surgery patients. All patients were evaluated at rest, during a procedure, and 20 minutes after a procedure (Gelinas 2006). The CPOT has been tested in over 500 medical, surgical, neurologic, and trauma patients. Although the CPOT was originally developed in French, it has been translated into English, Spanish, and Swedish. The CPOT has the advantage that it can be used in both ventilated and nonventilated, nonverbal patients. Implementing CPOT has resulted in more pain assessments and better use of analgesic and sedative agents. Limitations of the CPOT include that the vocalization component for nonintubated, nonverbal patients has only been validated in postoperative cardiovascular surgery patients. Thus, further testing is needed in nonverbal, nonventilated patients such as those with delirium or cognitive deficits (Gelinas 2013).

Vital signs should not be used alone to assess pain but rather as a cue to further assessment using the PAD guidelines. Observational studies have had several limitations and provided inconsistent results for assessing pain in medical, surgical, and trauma patients. Vital signs increase during nociceptive and nonnociceptive procedures or remain unchanged during nonnociceptive procedures. Furthermore, vital signs do not correlate with patients' self-reports of pain (Barr 2013a).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Etiology, pathophysiology, and risk factors associated with pain, agitation, and delirium (PAD)
- Nonpharmacologic strategies used in the prevention and treatment of PAD
- Different characteristics and adverse effects of pharmacologic agents used in the treatment of PAD

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- Society of Critical Care Medicine. 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit.
- ICU Delirium and Cognitive Impairment Study Group [homepage on the Internet].
- ICU Liberation [homepage on the Internet].

SEDATION-AGITATION MONITORING

The PAD guideline committee evaluated 27 studies including 2805 patients. The psychometric quality analysis used 10 subjective sedation scales to evaluate the depth and quality of sedation in adult ICU patients: Observer's Assessment of Alertness/Sedation (OAA/S) scale, Ramsay Sedation Scale (Ramsay), new Sheffield Sedation Scale (Sheffield), Sedation Intensive Care (SEDIC) score, Motor Activity Assessment Scale (MAAS), Adaptation to the Intensive Care Environment (ATICE), Minnesota Sedation Assessment Tool (MSAT), Vancouver Interaction and Calmness Scale (VICS), Sedation-Agitation Scale (SAS), and Richmond Agitation-Sedation Scale (RASS). The SAS and RASS both received scoring that indicated very good psychometric quality. In addition, moderate to high correlations were found between the RASS and SAS and electroencephalogram (EEG) or bispectral index (BIS) values (Barr 2013a). As a result of this evaluation, the 2013 PAD guidelines recommend the SAS and RASS as the most valid and reliable tools for assessing the quality and depth of sedation in adult ICU patients (Barr 2013a).

Table 2-1. Behavioral Pain Scale

Indicator	Description	Score
Facial expression	Relaxed	1
	Partly tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partly bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilator	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Cannot control ventilation	4
Total points		3–12 (A score > 5 in nonverbal ICU adult patients is predictive of significant pain)

Information from: Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

The SAS (Table 2-3) was developed by an interprofessional group consisting of a physician, a nurse, and a pharmacist from Maine Medical Center. The SAS was validated in a 34-bed medical and surgical ICU at a nonuniversity, academic medical center. Forty-five patients were assessed to provide 69 paired evaluations. Evaluators used the SAS to determine interrater reliability and compared it with the Ramsay and Harris scales to verify validity. Using the SAS, 45% of patients were classified as anxious or agitated (SAS 5–7), 26% were calm (SAS 4), and 29% were sedated (SAS 1–3). The SAS's interrater correlation was high (r^2=0.83; p<0.001), and the weighted kappa statistic for interrater agreement was 0.92 (p<0.001). From the assessments that scored as a Ramsay 1, 49% were SAS 6, 41% were SAS 5, 5% were SAS 4, and 2% were SAS 3 or 7. Correlation was high between the SAS and the Ramsay (r^2=0.83, p=0.001) and Harris (r^2=0.86, p<0.001) scales (Riker 1999).

The RASS (Table 2-4) was developed by an interprofessional group of physicians, a pharmacist, and nurses from the Medical College of Virginia. The RASS takes 20 seconds to perform and requires minimal training. The RASS was originally validated at the Medical College of Virginia in 172 patients, including medical, surgical, neurosurgical, and cardiac ICU patients, resulting in 192 patient encounters. Interrater reliability was excellent (r=0.956, lower 90% confidence limit 0.948; κ = 0.73; 95% CI, 0.71–0.75) between the five investigators (two physicians, two nurses, and one pharmacist). In patients with and without mechanical ventilation or sedation, interrater reliability was robust (r=0.922–0.983) (κ = 0.64–0.82). Correlation was high (r=0.93) between the RASS and a visual analog scale. After implementing the RASS in the medical ICU at the Medical College of Virginia, interrater reliability was high (r=0.964; lower 90% confidence limit 0.950; κ = 80; 95% CI, 0.69–0.90) between 1 nurse educator and 27 trained bedside nurses in 101 patient encounters. In addition, the validity of the RASS was confirmed with a correlation between the RASS and the Ramsay sedation scale (r= -0.78) and the SAS (r=0.78) (Sessler 2002). The RASS was further validated in 275 adult medical and coronary ICU patients from 38 ICUs. The RASS had excellent interrater reliability, construct, criterion, and face validity (Ely 2003). The feasibility of the RASS is shown by its consistent demonstration of a consensus target for goal-directed delivery of sedatives (Barr 2013a).

The PAD guidelines recommend that analgosedation or sedation be titrated to maintain a light level of sedation (RASS of 0 to -1 or SAS of 4) unless clinically contraindicated (Barr 2013a). The clinician chooses a target RASS or SAS for sedation titration to avoid over- and under-sedation, in which sedating medications are titrated (if under-sedated) or tapered (if over-sedation) according to the patient's actual RASS or SAS. This strategy enables the bedside clinician to evaluate a patient's level of consciousness and obtain information to evaluate the patient for delirium. Each drug used for analgosedation or sedation must also be ensured to have the same RASS or SAS target.

The PAD guidelines do not recommend using objective measures of brain function (e.g., auditory evoked potentials,

Table 2-2. Critical-Care Pain Observation Tool

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense 1
	All of the above facial movements plus eyelid tightly closed	Grimacing 2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements 0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection 1
	Pulling tube, trying to sit up, moving limbs, thrashing, not following commands, striking at staff; trying to climb out of bed	Restlessness 2
Muscle tension	No resistance to passive movements	Relaxed 0
	Resistance to passive movements	Tense, rigid 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid 2
Compliance with the ventilator (ventilated patients) OR Vocalization (extubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or making no movement 0
	Alarms stop spontaneously	Coughing but tolerating 1
	Asynchrony; blocking ventilation, alarms often activated	Fighting ventilator 2
	Talking in normal voice or no sound	Talking in normal voice or making no sound 0
	Sighing, moaning	Sighing, moaning 1
	Crying out, sobbing	Crying out, sobbing 2
Total range of points		0–8 (A score > 2 in nonverbal ICU adult patients is predictive of significant pain)

Information from: Gelinas C, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care 2006;15:420-7; and Gelinas C, Johnston C: Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin J Pain 2007;23:497-505.

Bispectral Index, Narcotrend Index, Patient State Index, state entropy) in non-comatose adult patients who are not receiving neuromuscular blockade. These objective measures were deemed adequate substitutes from subjective scoring. However, objective measures are recommended to measure the depth of sedation in adult ICU patients who are receiving neuromuscular blocking agents (Barr 2013a).

DELIRIUM MONITORING

Routine monitoring for delirium is recommended by the 2013 PAD guidelines (Barr 2013a). Delirium is present in 60%–80% of mechanically ventilated patients and in 20%–50% of non-mechanically ventilated patients. If delirium is not monitored for with a structured tool, it will be unrecognized in three of four patients (Brummel 2013).

The 2013 PAD guidelines committee performed a psychometric quality evaluation of the five different delirium monitoring tools: cognitive test for delirium (CTD), confusion assessment method for the ICU (CAM-ICU), Delirium Detection Score (DDS), Intensive Care Delirium Screening Checklist (ICDSC), and Nursing Delirium Screening Scale (Nu-DESC). Both the CAM-ICU and the ICDSC scoring indicated very good psychometric quality. As a result of this evaluation, the 2013 PAD guidelines recommend the CAM-ICU and the ICDSC as

Table 2-3. Riker Sedation-Agitation Scale

Score	Term	Descriptor
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commends but drifts off again
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Guidelines for SAS assessment:

1. Agitated patients are scored according to their most severe degree of agitation.
2. A patient who is awake or who awakens to voice easily (responds with voice or head shaking to a question or follows commands) is SAS 4 (patient can even be napping).
3. A patient who requires stimuli such as shaking but eventually awakens represents SAS 3.
4. The patient who arouses to stronger physical stimuli but never awakens to be able to respond yes/no or follow commands represents SAS 2.
5. A patient who never awakens and noxious physical stimuli result in little or no response is SAS 1.

Information from: Riker RR, Picard JT, Fraser GL: Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325-9; and Brandt KM, Langley KA, Riker RR, et al. Confirming the reliability of the sedation-agitation scale administered by ICU nurses without experience in its use. Pharmacotherapy 2001;21:431-6; www.icudelirium.org.

Table 2-4. Richmond Agitation-Sedation Scale

Scale	Label	Description
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls to remove tubes of catheters; aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive movements; not aggressive
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact > 10 s)
-2	Light sedation	Briefly awakens to voice (eyes open and contact < 10 s)
-3	Moderate sedation	Movement or eye opening to voice (no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Information from: Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44; and Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983-91.

the most valid and reliable monitoring tools for delirium in adult ICU patients (Barr 2013a).

Confusion Assessment Method for the ICU

The CAM-ICU (Figure 2-1), adapted from the Confusion Assessment Method (CAM), assesses the four key diagnostic features of delirium: (1) acute change or fluctuation in mental status from baseline, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking (Ely 2001a, 2001b; Inouye 1990). The order of the CAM-ICU is very logical and promotes efficiency. A patient must meet the criteria for both acute change or fluctuating course of mental status (feature 1) and inattention (feature 2) to be given a diagnosis of delirium. If the patient does not meet both criteria, altered level of consciousness (feature 3) and disorganized thinking (feature 4) need not be assessed. In addition, disorganized thinking (feature 4) must be assessed only when a patient meets the criteria for acute change or fluctuating course of mental status (feature 1) and inattention (feature 2) but does not meet the criteria for altered level of consciousness (feature 3). The subsyndromal delirium criteria are met when a patient meets the criteria for features 1 and 4 only or feature 2 only (Brummel 2013). The online CAM-ICU training manual provides detailed information on performing the CAM-ICU. Box 2-1 lists additional tips on performing each feature of the CAM-ICU.

The CAM-ICU was originally validated at Vanderbilt University Medical Center in 96 adult patients admitted to a medical or coronary ICU. There were 471 paired evaluations performed daily by two critical care study nurses and compared with assessments by delirium experts using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Compared with the reference standard used for diagnosing delirium, the two nurses using the CAM-ICU had a sensitivity of 100% and 93%, specificity of 98% and 100%, and high interrater reliability (κ = 0.96; 95% CI, 0.92–0.99) (Ely 2001b).

Intensive Care Delirium Screening Checklist

The ICDSC is an 8-item checklist used over a longer period (8–24 hours) in which 1 point is given for each checklist item present. The eight symptoms are level of consciousness, inattention, disorientation, hallucinations/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbances, and symptom fluctuation. A score of 4 points or more is consistent with delirium, whereas a score of 1–3 indicates subsyndromal delirium (Bergeron 2001). Table 2-5 provides specific suggestions for assessing each component of the checklist.

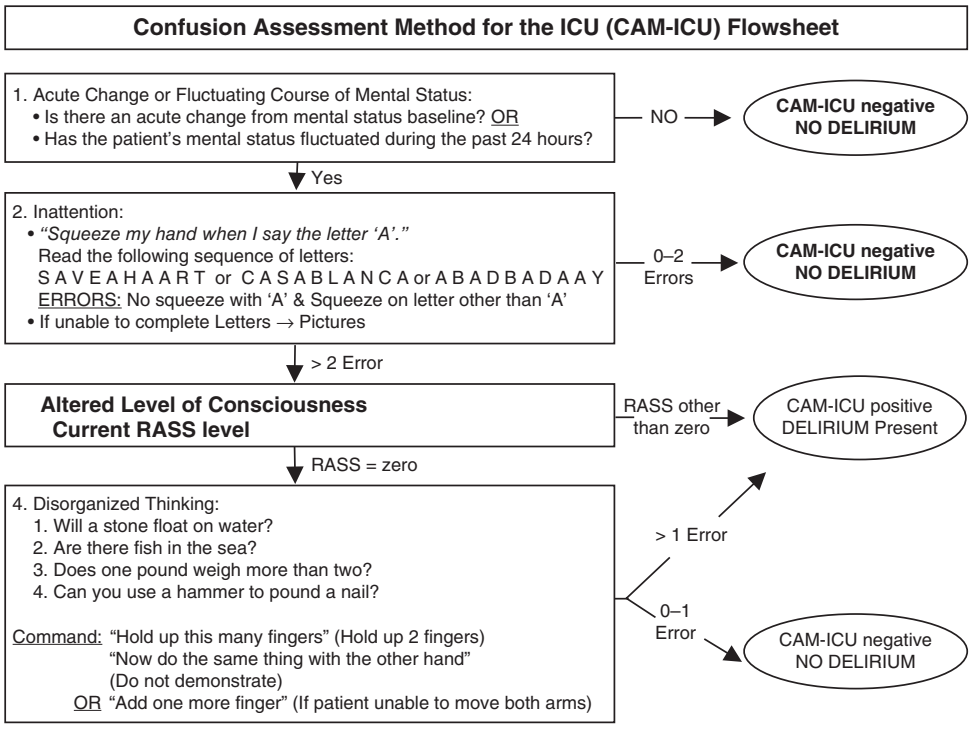

Figure 2-1. Confusion assessment method for the ICU.

Box 2-1. Tips for Performing the Features of the CAM-ICU

Feature 1: Acute Change or Fluctuating Course of Mental Status

What if you do not know the patient's baseline?

- Assume normal unless "red flags"
- Red flag: Patient came from a long-term care facility or nursing home institution

Has the patient's mental status fluctuated over the past 24 hours, as assessed by the RASS or SAS?

Feature 2: Inattention

SAVE A HAART

- Caregivers instruct the patient to squeeze their hand every time the patient hears the letter A
- If the patient squeezes on every letter, the criteria for inattention are met
- If the patient does not squeeze on any letter, the criteria for inattention are met

Visual attention test

- Pictures are more rigorous stress tests of attention needed in < 5% of patients who cannot complete SAVE A HAART because of a physical limitation or inability to squeeze hand
- Patient is shown five pictures and asked to remember these. Patient is then shown 10 pictures and told to state whether picture was previously seen (picture cards and instructions available at www.icudelirium.org/assessment.html)
- If the patient makes > 2 mistakes, the patient meets the criteria for inattention

Feature 3: Altered Level of Consciousness

- Consider performing this feature first to avoid touching the patient first before assessing RASS

Feature 4: Disorganized thinking

- Each question counts as 1 point, and the full command counts as 1 point
- If the patient makes > 1 error, the criteria for disorganized thinking are met
- An alternative set of questions is at www.icudelirium.org

Information from: Brummel NE, Vasilevskis EE, Han JH, et al. Implementing delirium screening in the ICU: secrets to success. Crit Care Med 2013;41:2196-208.

The ICDSC was originally validated in 93 patients at Hôpital Maisonneuve-Rosemont in Montreal, Quebec, Canada. An ICU physician evaluation was compared with a psychiatry evaluation. The sensitivity and specificity of the ICDSC was evaluated using a receiver operating characteristic (ROC) analysis. The area under the ROC curve was 0.9017; the ICDSC's predicted sensitivity was 99% and specificity was 64% (Bergeron 2001).

DIFFERENCES BETWEEN THE CAM-ICU AND THE ICDSC

The two main differences between the CAM-ICU and the ICDSC are the period in which the symptoms are assessed and the method by which the delirium symptoms are identified. Using the CAM-ICU, an episode of delirium may be missed, given the fluctuating course of delirium. This may be an issue, partic ularly in patients with a lower severity of illness. However, increasing the frequency and performing CAM-ICU assessments with mental status changes may address this limitation. A possible limitation of the CAM-ICU is that performance may rely on the patient's age, prior medical conditions, and severity of illness; however, in the original validation study, performance was reliable across all the aforementioned subgroups. The ICDSC depends on observation for detecting many of the eight checklist items; recognizing these symptoms may be difficult in nonverbal, mechanically ventilated patients, requiring subjective interpretation (Brummel 2013).

RECOGNITION OF HYPOACTIVE DELIRIUM

A common misconception is that all patients with delirium are hallucinating and delusional: neither of these symptoms is required to make the diagnosis. The two types of delirium are (1) hyperactive, characterized by delusions and hallucinations: and (2) hypoactive, characterized by confusion and sedation. Patients may fluctuate between hyperactive and hypoactive delirium; this is termed *mixed delirium*. Hypoactive delirium is often undiagnosed if a validated assessment tool is not used (Barr 2013a).

ABCDEF BUNDLE

Although decades of research have shown the harm associated with ICU-acquired delirium and weakness, these two conditions are still often unrecognized in the ICU. A six-step approach called the ABCDEF bundle (Box 2-2). The bundle includes interventions to decrease sedation exposure, duration of mechanical ventilation, and ICU-acquired delirium and weakness (Balas 2013; Vasilevskis 2010). These interventions are ideally performed by an interprofessional team that includes physicians, nurses, pharmacists, respiratory therapists, and physical and occupational therapists. Each part of the ABCDEF bundle is evidence based, helps standardize communication, decreases mortality, and improves long-term cognitive and functional outcomes. This bundle enables the focus of care to be on patients and families.

Table 2-5. Intensive Care Delirium Screening Checklist

- Score your patients over the entire shift. Components need not be present at the same time
- A focused bedside patient assessment is required for components 1–4. If patients are deeply sedated or comatose (i.e., SAS = 1 or 2 or RASS = -4 or -5), this cannot be completed
- Observations throughout the shift allow assessment of components 5–8. For components 7 and 8, information from the prior 24 hours should be used

Item	Assessment
1. Altered level of consciousness	"1" for either of the following: • RASS +1 to +4 or -1 to -3 • SAS 3 or 5 to 7 "0" for either of the following: • RASS 0 or -1 to -3 related to recent sedation or analgesia • SAS 4 or 3 related to recent sedation/analgesia If patient is SAS 1 to 2 or RASS -4 to -5, the ICDSC cannot be assessed
2. Inattention	"1" for any of the following: • Difficulty following instructions or conversation, • Easily distracted by external stimuli • Will not reliably squeeze hands to spoken letter A: SAVE A HAART
3. Disorientation	"1" if the patient cannot recognize caregivers in addition to name, place, and date or that he/she is in the hospital
4. Hallucination, delusion, or psychosis	"1" for either of the following: • Is the patient having delusions or hallucinations (e.g., trying to catch an object that is not there) • Is the patient afraid of people or things around them?
5. Psychomotor agitation or retardation	"1" for either of the following: • Potentially dangerous behavior requiring the use of sedatives or restraints (e.g., pulling out intravenous lines or hitting staff) • Clinically noticeable or hypoactive psychomotor slowing or retardation not attributable to opiate or sedative administration
6. Inappropriate speech or mood	"1" for either of the following: • Inappropriate emotion, disorganized or incoherent speech • Inappropriate mood related to events or situations
7. Sleep-wake cycle disturbance	"1" for any of the following: • Sleeping < 4 hr sleep at night • Waking frequently at night (if not attributable to being awoken by medical staff or a loud environment) • Sleeping ≥ 4 hours during the day
8. Symptom fluctuation	"1" for fluctuation in any of the above symptoms over a 24-hr period
Total Shift Score (0–8)	A score ≥ 4 is consistent with delirium, whereas a score of 1–3 indicates subsyndromal delirium

RASS = Richmond Agitation-Sedation Scale; SAS = Sedation-Agitation Scale.

Information from: Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859-64; and Ouimet S, Riker R, Bergeron N, et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. Intensive Care Med 2007;33:1007-13.

Box 2-2. Components of the ABCDEF Bundle

- Assess, prevent, and manage pain
- Both SATs and SBTs
- Choice of analgesia and sedation
- Delirium assessment, treatment, and management
- Early mobility and exercise
- Family engagement and empowerment

A multicenter, prospective, cohort, before-after study of 296 patients (146 pre-bundle and 150 post-bundle) treated with the ABCDE bundle found that patients spent 3 fewer days on the ventilator (median [interquartile range], 24 [7–26] vs. 21 [0–25]; p = 0.04). In addition, after adjusting for age, sex, severity of illness, comorbidity, and mechanical ventilation, patients treated with the ABCDE bundle had a significant decrease in the odds of delirium (OR 0.55; 95% CI, 0.33–0.93; p = 0.03) (Balas 2014; Balas 2013; Vasilevskis 2010).

Despite the known benefits of each component of the ABCDEF bundle and use of the recommendations in the PAD guidelines, many institutions do not routinely perform these interventions in clinical care. During the aforementioned 18-month study of the ABCDE bundle, the interprofessional team members responsible for conducting the bundle identified facilitators and barriers to implementation. Factors identified as facilitating included incorporation of daily interprofessional rounds, involvement of key implementation leaders, continued and varied educational opportunities, and the bundle's quality and strength. Factors perceived as barriers included intervention-related concerns (e.g., timing of trials, concern for adverse events), lack of communication and the challenge of care coordination, knowledge deficits, concern with performing interventions during a busy ICU shift, and increased documentation. Despite the challenges associated with implementing the ABCDE bundle, participants thought the bundle benefited the patient, promoted interprofessional communication, and empowered ICU team members (Balas 2013). In addition, SCCM has begun a program called the ICU Liberation ABCDEF Bundle Improvement Collaborative to aid in implementing the PAD guidelines in 77 U.S. hospitals that are committed to improving patient and family outcomes.

Several successful intervention studies implemented various components of the ABCDEF bundle, highlighting the important role of pharmacists. The spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT) are key bundle components that prevent oversedation, prolonged intubation, delirium, and subsequent weakness. The multicenter, prospective Awakening and Breathing Controlled (ABC) trial randomized 336 ventilated patients to the SAT coordinated with the SBT (ABC group) versus the SBT plus sedation by usual care. The ABC group spent 3 fewer days on mechanical ventilation, 3 fewer days in the ICU, and 5 fewer days in the hospital. The ABC group also had a 14% improvement in 1-year survival (HR 0.68; 95% CI, 0.5–0.92; p=0.01) (Girard 2008).

The multicenter, prospective SLEAP study randomized 430 ventilated patients to protocolized sedation versus protocolized sedation plus the SAT. The median time to extubation was 7 days in both the control and SAT groups; the duration of ICU and hospital stay did not differ between groups; the SAT group did not achieve a decrease in psychoactive drugs (benzodiazepine administration increased); and the passing of the SBT did not routinely result in extubation (Mehta 2012).

Often the SAT and SBT may not be performed or is not properly performed or coordinated between disciplines (Patel 2009; Mehta 2006). The current conundrum is not whether SATs and SBTs are beneficial, but rather, finding ways to ensure their daily performance and coordination among several disciplines. The results of the SLEAP study highlight why process measures are so important. The "Wake Up and Breathe" protocol (Figure 2-2) used in the ABC study lists the safety screen for performing SATs and SBTs daily, providing an excellent tool for instructing clinicians how to proceed through the ABC process daily. Box 2-3 lists recommendations for implementing the ABC protocol in the ICU.

There are examples of successful strategies for implementing SATs and SBTs in the ICU. In a pharmacist-driven ABC quality improvement (QI) program, the pharmacist provided educational sessions to nursing staff before initiating the QI program on their role in initiating the SAT and coordinating the SBT with the respiratory therapist. During the QI program, the pharmacist ensured daily discussion of the SAT/SBT on interprofessional rounds; made sure the SAT was performed correctly; ensured that intermittent analgesia was ordered and administered, if warranted; confirmed performance and coordination of the SBT by the nurse and respiratory therapist; and provided weekly unit performance reports. The rates of safety screening, performance of SATs and SBTs, and coordination of the SAT and SBT all significantly improved in the pre-QI and during-QI groups. These efforts were also sustained during the 8-month post-QI follow-up (Stollings 2015).

The ABC protocol was implemented in a pre/post-implementation study of 702 consecutive mechanically ventilated patients in a mixed medical/surgical ICU. Multidisciplinary weekly group meetings were held over 3 months to develop the ABC protocol and train the ICU staff. After implementing the ABC protocol, mean RASS scores increased by 0.88 (p<0.0001) on weekdays and 1.21 (p<0.0001) on weekends. The combined prevalence of delirium/coma was reduced from 90.8% to 85% after implementing the ABC protocol (OR 0.505; 95% CI, 0.299–0.853; p=0.01) (Khan 2014).

A multicenter QI initiative to perform the ABC protocol was nested within a prospective study of ventilator-associated events (VAEs) in 20 ICUs. Twelve ICUs implemented an ABC protocol, whereas eight ICUs conducted surveillance only. The Institute for Healthcare Improvement's "all-teach, all-learn" framework was used by the 12 collaborative units.

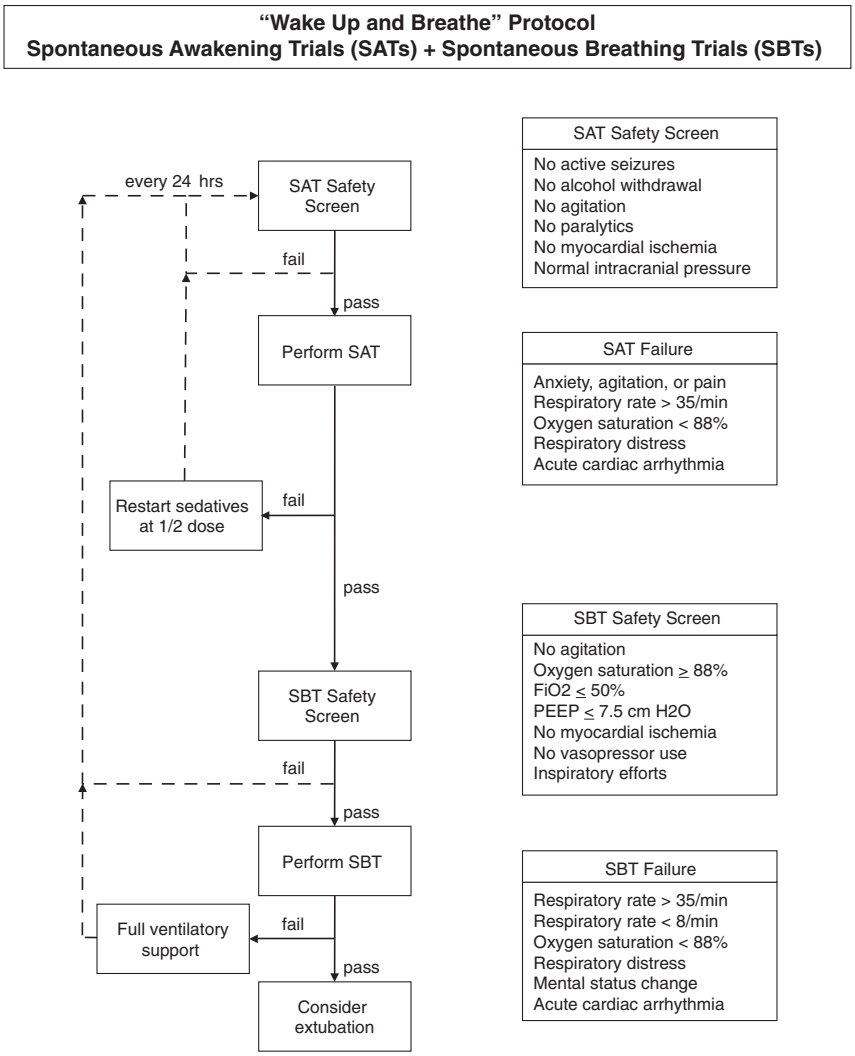

Figure 2-2. "Wake Up and Breathe" protocol.

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Each unit chose a physician, nurse, and respiratory therapist to be a clinical champion and collaborative liaison. The CDC conducted an in-person meeting to review the ABC protocol, design unit-specific goals, and plan interventions. The plan-do-study-act cycles were used to encourage making small tests of changes. Clinical champions prepared monthly reports of successes and challenges from the previous month and set goals for the upcoming month. Monthly web conferences were held to discuss successes and challenges, and an e-mail list was available to enable discussion between monthly meetings. Monthly performance reports were provided to each unit, as well as de-identified statistics from other units to allow peer comparison among groups. A total of 3425 consecutive episodes of mechanical ventilation were collected in the collaborative units, and 1739 were collected in the surveillance-only units. The collaborative group had a significant increase in SATs and SBTs and a decrease in duration of mechanical ventilation and hospital length of stay after implementing the ABC protocol. No change was found in VAE risk per day or prevalence of pneumonias. However, there was a significant decrease in VAE risk per episode of mechanical ventilation (OR 0.63; 95% CI, 0.42–0.97) and infection-related ventilator-associated complications (OR 0.35; 95% CI, 0.17–0.71). No differences in SATs, SBTs, or VAEs were found in the surveillance-only units (Klompas 2015).

In a multidisciplinary process improvement project in two 10-bed medical ICUs, the ABC protocol was implemented. A training team composed of critical care pharmacists, ICU nurse educators, and a pulmonary fellow provided 15-minute educational sessions that included both didactic lectures and

Box 2-3. Recommendations for Implementing the ABC Protocol in the ICU

1. Use an interprofessional team
   - Physicians, nurses, pharmacists, and respiratory therapists can serve as experts and resources throughout implementation
   - Physician champion
   - Include ICU leadership to sell the implementation during interprofessional rounds
2. Determine what time of day this will occur
   - Consider having the night shift conduct the safety screen just before the end of shift (e.g., 6:30 a.m.)
   - Consider having the day shift perform the SAT if the patient meets the safety screen during the initial patient assessment after receiving the report from the night nurse (e.g., 7:30 a.m.)
   - Screen the criteria after pass-off from the night-shift nurse has occurred
   - Have the nurse contact the respiratory therapist once the SAT is started to perform the SBT safety screen and SBT
   - This enables discussion during rounds if the SAT or SBT was inappropriately performed
   - This enables appropriate patients to be extubated during interprofessional rounds
3. Empower the nurse and respiratory therapist by implementing a protocol
   - Promotes autonomy
   - Eliminates the need for physician or mid-level provider order
4. Ensure that "as-needed" doses of analgesics are ordered for all patients on continuous analgesia or sedation
   - Enables the nurse to give intermittent analgesia first once continuous sedation and analgesia have been stopped before having to restart the continuous sedation or analgesia at half the previous dose
5. Use many approaches to teach nurses to perform the SAT
   - Didactic lectures
   - Pocket cards
   - Case-based scenarios
   - Individual training by ABC champions
   - Providing the unit with weekly performance reports
6. Follow-up training
   - Continual feedback and encouragement
   - Train all new staff at orientation, and give refresher courses to current staff
   - Spot checking documentation and appropriate performance
7. Presenting ABC in interprofessional rounds
   - Brain road map (see Table 2-7)
8. Determine how often used and where documentation in the EMR should occur
   - Consider having the night-shift nurse document the SAT safety screen
   - Consider having the day-shift nurse document SAT performance and whether passed
   - Respiratory therapist should document the SBT safety screen, SBT performance, and whether passed
   - Determine where in the EMR the SAT/SBT safety screen and performance results will be recorded to facilitate communication among staff

EMR = electronic medical recond; SAT = spontaneous awakening trial; SBT = spontaneous breathing trial.

Information from: Stollings JL, Foss JJ, Ely EW, et al. Pharmacist leadership in ICU quality improvement: coordinating spontaneous awakening and breathing trials. Ann Pharmacother 2015;49:883-91.

bedside teaching to all nurses, respiratory therapists, pulmonary fellows, attending physicians, and rotating house staff on the ABC protocol. A validated 12-point quiz was administered to all nurses in each unit after education. Any new providers who came on service after the initial training period received the same education. In the intervention group, 44% of patients had SATs, and 84% of patients had SBTs. The intervention group received continuous infusions of sedatives on fewer days of mechanical ventilation than the control group (67% vs. 100%, p=0.003). The intervention group also had sedation tapered by greater than 25% on more days than the control group (71% vs. 40%, p=0.006). Total amount of continuous sedation administered (p=0.49), total days of mechanical ventilation (p=0.75), days in which an SAT occurred (p=0.38), and episodes of self-extubation (p=0.43) did not differ between the intervention and control groups (Kher 2013).

Choice of analgesia and sedation is a key part of the ABCDEF bundle and one in which pharmacists can play a large role. The

PAD guidelines recommend using non-benzodiazepine sedation strategies (e.g., propofol or dexmedetomidine) to improve clinical outcomes in mechanically ventilated patients (Barr 2013a).

There are several examples of successful strategies for implementing sedation protocols in the ICU. In a prospective QI project to decrease sedation and delirium, mechanically ventilated patients with acute lung injury in a 16-bed medical ICU were assessed. A new sedation protocol was created that recommended a target RASS score of 0 and required patients' use of intermittent sedation to fail before using continuous infusions. Delirium screening with the CAM-ICU was also initiated twice daily. The previous sedation protocol in the medical ICU had used goal-directed sedation and a 50% daily reduction in fentanyl and midazolam rather than complete interruption. The "4Es" framework (i.e., engage, educate, execute, and evaluate) was used to implement the QI process. The QI team consisted of the medical ICU nurse educator, a pharmacist, three physicians, two psychiatrists, and a rehabilitation neuropsychologist. The median proportion of days on continuous infusions of narcotics (33% vs. 74%, p<0.001) and sedatives (22% vs. 70%, p<0.001) was significantly lower in the QI group than in the control group. The median RASS was also increased in the QI group compared with the control group (median RASS score per patient -1.5 vs. -4.0, p<0.001). A greater median proportion of medical ICU days per patient without sedation (RASS +1, 0, or -1) occurred in the QI group than in the control group (50% vs. 20%, p<0.001). The number of days awake and free of delirium in the medical ICU also increased in the QI group compared with the control group (median 19% vs. 0%, p<0.001). However, the QI group had a greater median proportion of days per patient with delirium than the control group (38% vs. 20%, p=0.01) (Hager 2013).

In a before-after study, the effect of daily pharmacist interventions to promote adherence to sedation guidelines was documented on clinical outcomes in two medical ICUs. Pharmacists made interventions according to the SAS goal, identification of pain and delirium, laboratory testing, and organ dysfunction. All pharmacists involved in the study, except for the study investigators, had completed 1 month of training before study involvement and reviewed all pertinent literature. The mean duration of mechanical ventilation was decreased from 338 ± 348 hours (14 days) in the control group compared with 178 ± 178 hours (7.4 days) in the intervention group (p<0.001). Both ICU stay (380 ± 325 hours vs. 238 ± 206 hours, p=0.001) and hospital stay (537 ± 350 hours vs. 369 ± 274 hours, p=0.001) were significantly decreased in the intervention group (Marshall 2008).

A multidisciplinary pre-post study examined the effects of implementing a pain, sedation, and delirium protocol in a mixed medical and surgical ICU. Nurses were trained how to use and record results from numeric rating scales for pain, BPS, RASS, and ICDSC. All new nurses were educated on the screening tools. Nurses were also educated to offer patients the opportunity to listen to music or receive sedative medications and to provide reorientation to patients with delirium. Physicians were instructed to use a protocol that guided the prescribing of drugs for PAD according to the earlier-listed assessments. The intervention group received fewer opiates (90.72 ± 207.45 vs. 22.93 ± 40.36 morphine equivalents/day, p<0.0001). Sedation was comparable between the control and intervention groups, but the intervention group had a shorter duration of mechanical ventilation. Also, drug-induced coma (18.1% vs. 7.2%, p<0.0001), ICU and hospital length of stay, and dependency at discharge were all lower in the intervention group. The presence of delirium was similar between groups, although subsyndromal delirium was significantly decreased in the intervention group. Mortality at 30 days was higher in the control group than in the intervention group (29.4% vs. 22.9%, p=0.009) (Skrobik 2010).

Implementation and routine use of the CAM-ICU or ICDSC is the centerpiece to delirium detection, prevention, and treatment. Using a standardized tool prevents overdiagnosis of delirium in a patient who is agitated without delirium and prevents underdiagnosis in a patient who has hypoactive delirium (Guenther 2012; Spronk 2009). Box 2-4 lists recommendations for implementing delirium screening in the ICU and barriers that can be overcome through education.

There are examples of successful strategies for implementing delirium screening in the ICU. In a prospective, multicenter, observational study, level of consciousness (RASS) and delirium monitoring (CAM-ICU) in two medical ICUs were implemented. A 20-minute, unit-wide, introductory inservice describing the RASS and CAM-ICU, including pocket card distribution and case studies, was provided to all ICU nurses. Over the next 6–9 months, additional education was provided through monthly staff meetings, display of unit-wide performance data, and one-on-one teaching with a delirium champion. Compliance with the RASS was greater than 94%, and compliance with the CAM-ICU was greater than 84% at both institutions over the next 6–12 months. High agreement was found between the bedside nurses and the expert raters in both ICUs for both the RASS and the CAM-ICU (Pun 2005).

A separate study addressed the barriers to screening for delirium, including lack of communication between health care workers on the ICU team, differences in shifts, high workload, and part-time nurses, before initiating the implementation process. The number of nursing shifts in which a delirium screening occurred increased from 38% to 95% after implementation (Riekerk 2009).

In a prospective, observational study of a level 1 trauma unit of a tertiary medical center, delirium monitoring, web-based teaching modules, group inservices, and individualized demonstrations were implemented over 2 weeks to educate staff on RASS and CAM-ICU assessments. This was followed up by 10 weeks of "spot checking" and informal education led by nurse champions, after which an expert evaluator determined the compliance and reliability of the CAM-ICU in trauma patients. The overall agreement (κ=0.77) between bedside nurses and expert raters was high. The CAM-ICU was

Box 2-4. Recommendations for Implementing Delirium Screening in the ICU

1. Use an interprofessional team
   - Physicians, nurses, pharmacists, respiratory therapists, occupational and physical therapists that serve as experts and resources throughout implementation
   - Physician champion
   - Include ICU leadership to sell the implementation during interprofessional rounds
2. Choose either the CAM-ICU or the ICDSC
3. Pair with the SAS or RASS
4. Identify common barriers to implementing delirium screening
   - Lack of understanding of prevalence of delirium
   - Caregivers having difficulty using a tool
   - Feasibility of conducing delirium assessments in a busy ICU
5. Use several approaches to teach clinicians to screen for delirium
   - Didactic lectures
   - Pocket cards
   - Example screening videos on www.icudelirum.org
   - Case-based scenarios
   - Individual training by delirium champions
   - Providing the unit weekly performance reports
6. Provide follow-up training
   - Continual feedback and encouragement
   - Monthly staff meetings to reinforce screening concepts
   - Train all new staff at orientation and provide refresher courses to current staff
   - Spot checking
7. Present delirium screening results on interprofessional rounds Brain road map (Table 2-7)
8. Determine how often used and where documentation in the EMR should occur
   - Performance once per day or once per shift
   - Determine where in the EMR delirium screening results will be recorded to facilitate communication among staff

Information from: Brummel NE, Vasilevskis EE, Han JH, et al. Implementing delirium screening in the ICU: secrets to success. Crit Care Med 2013;41:2196-208; and Pun BT, Devlin JW. Delirium monitoring in the ICU: strategies for initiating and sustaining screening efforts. Semin Respir Crit Care Med 2013;34:179-88.

performed on more than 85% of nursing shifts in the 6 weeks after the implementation period ended (Soja 2008).

Case-based scenarios and didactic teaching were used to implement the ICDSC in two ICUs. After the intervention, the number of bedside nurses who could correctly and accurately assess for delirium using the ICDSC increased (Devlin 2008). A second pharmacist-led intervention determined the effect of providing delirium education and implementing the ICDSC on surgical-trauma ICU nurses' ability to perform accurate delirium assessments. Live presentations, web-based tutorials, and bedside demonstrations improved nurses' knowledge of delirium and accuracy of ICDSC performance (Gesin 2012).

A pharmacist in a surgical ICU used a before-after study to determine the incidence of inappropriate CAM-ICU "unable to assess" ratings before and after educational sessions. Three nurse educators provided 10 minutes of bedside, one-on-one education to bedside nurses in the intervention group. After the educational efforts, patients were 41% less likely to receive an inappropriate "unable to assess" rating (32% control group vs. 19% intervention group, p=0.03). Patients receiving mechanical ventilation were more likely to receive inappropriate "unable to assess" ratings in the control group (OR 30.7; 95% CI, 8.9–105.9; p<0.001) than were patients in the intervention group (OR 15.5; 95% CI, 4.1–59.5; p<0.001) (Swan 2014).

The brain road map (Table 2-6) is a quick and efficient way for the bedside nurse to communicate a patient's PAD. This allows the interprofessional team to quickly communicate about the patient's current degree of pain, level of consciousness, and delirium and to determine how best to manage these identified components of the patient's ICU care (Pun 2013).

Early mobility is an integral part of the ABCDEF bundle and has been the only intervention shown to decrease days of delirium; it consists of activities from passive range of motion to ambulation. Early mobility can be performed by any part of the interprofessional team (e.g., nurses, physical therapists, occupational therapists, physicians). With the shortage of physical and occupational therapists at many institutions—and the busy schedules of nurses, physicians, and mid-level providers—early mobility is an important way to involve the family in patient care. Although pharmacists are not the logical team members to perform early mobility, they can recommend consulting with physical/occupational therapy during interprofessional rounds by remembering the safety criteria for performing physical therapy (Box 2-5).

In a prospective, randomized, multicenter study of 104 mechanically ventilated patients who were expected to stay ventilated for more than 24 hours, 49 patients were randomized to exercise mobilization, and 55 received standard care.

Table 2-6. Brain Road Map: Script for Reporting PAD on Interprofessional Rounds

Questions	Report
Where is the patient going?	Target scores: RASS/SAS
Where is the patient now?	Actual assessment scores: CPOT/BPS RASS/SAS CAM-ICU/ICDSC
How did the patient get here?	What medications does the patient currently receive or has the patient recently received for PAD?
Points for discussion	Is the patient's pain adequately controlled? Is the target RASS or SAS appropriate? What nonpharmacologic or pharmacologic therapies need to be considered for delirium? Do any medications need to be stopped or reduced? Do any medications need to be started (i.e., is the patient withdrawing from any medications before admission that have not been resumed)?

BPS = Behavioral Pain Scale; CPOT = Critical-Care Pain Observation Tool; PAD = pain, agitation, and delirium; RASS = Richmond Agitation-Sedation Scale; SAS = Sedation-Agitation Scale.

Information from: Brummel NE, Vasilevskis EE, Han JH, et al. Implementing delirium screening in the ICU: secrets to success. Crit Care Med 2013;41:2196-208; and ICU Delirium and Cognitive Impairment Study Group [homepage on the Internet].

Patient Care Scenario

W.J. is a 37-year-old woman who is admitted to the ICU with septic shock secondary to methicillin-resistant *Staphylococcus aureus* endocarditis. She is mechanically ventilated and receiving propofol at 50 mcg/kg/minute and fentanyl at 25 mcg/hour this morning. W.J. has the following mechanical ventilation settings: volume control, positive end-expiratory pressure 7 mm H_2O, fraction of inspired oxygen (Fio_2) 60%, and tidal volume 400 mL with Sao_2 93%. Her current drugs include famotidine 20 mg nasogastrically twice daily, enoxaparin 40 mg subcutaneously daily, and vancomycin 1000 mg intravenously every 12 hours. At baseline, W.J. works at the local diner, takes care of her three children, and attends nursing school. The patient is grimacing, pulling at her tube, and trying to sit up; she has strong resistance to passive movements and is coughing but tolerating the ventilator. She is anxious and apprehensive, but her movements are not aggressive. Her RASS has ranged from -3 to +2 over the past 24 hours. The patient's goal RASS is 0. When you assess W.J. for inattention using SAVE A HAART, she misses three of the letter A's. She answers all the questions in feature 4 correctly and completes the full command. What is the best approach to managing W.J.'s PAD?

ANSWER

W.J. is grimacing (2 points), pulling at her tube and trying to sit up (2 points), showing strong resistance to passive movements (2 points), and coughing but tolerating the ventilator (1 point). Her total CPOT score is 7 points, which indicates that she is in pain. Her RASS score is +1 because she is anxious and apprehensive, but her movements are not aggressive. W.J. meets the criteria for feature 1 (acute fluctuation in mental status) because her RASS fluctuates and is different from baseline. She meets the criteria for feature 2 (inattention) because she makes three mistakes in the SAVE A HAART. She meets the criteria for feature 3 (acute fluctuation in mental status) because her RASS is not 0. She does not meet the criteria for feature 4 (disorganized thinking) because she misses none of the questions and can complete the full command. The patient currently has PAD. Given that lack of treatment of pain can cause agitation and delirium, her fentanyl dose should be increased. With appropriate treatment of pain, she can hopefully be weaned off propofol. She does not currently meet the criteria for the spontaneous awakening trial (SAT) with her acute agitation. However, with treatment of her pain, she will hopefully be an appropriate candidate. The patient does not meet the criteria for the spontaneous breathing trial (SBT) with her Fio_2 of 60%. With appropriate treatment of pain, her delirium may improve. She is not an appropriate candidate for pharmacologic treatment of delirium at this time. Nonpharmacologic measures to prevent and treat delirium (e.g., physical therapy) should be implemented.

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
2. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 2014;5:1024-36.

Box 2-5. Inclusion Criteria to Perform Physical Therapy

Myocardial ischemia: Patient has had no acute myocardial ischemia or arrhythmia requiring treatment within the past 24 hr
Oxygenation inadequate: Patient must have Sao_2 > 88%, PEEP < 10 mm H_2O, and $FIO_2 \leq 60\%$
Vasopressors: The patient should not have had any vasopressors for 2 hr
Engagement to voice (lack of it): Patient must respond to verbal stimuli: RASS ≥ -3 or SAS ≥ 3

FIO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.

Fifty-nine percent of the intervention group returned to independent functional status at hospital discharge compared with 35% of the control group (p=0.02). The duration of delirium was 2 days in the intervention group compared with 4 days in the intervention group (p=0.02). Two additional ventilator-free days occurred in the intervention group compared with the control group (p=0.05) (Schweickert 2009).

In a randomized, single-center feasibility study (ACT-ICU) of 87 medical or surgical ICU patients with shock or respiratory failure, patients were randomized in a 1:1:2 ratio to usual care, early once-daily physical therapy, or early once-daily physical therapy in addition to twice-daily cognitive therapy. Ninety-five percent of patients randomized to the physical and cognitive therapy group received early cognitive therapy. No significant difference was found between groups in measures of executive function, global cognition, functional mobility, activities of daily living, instrumental activities of daily living, or health-related quality of life at the 3-month follow-up. No difference was found between groups in delirium/coma-free days, ventilator-free days, ICU length of stay, or hospital length of stay (Brummel 2012).

A prospective cohort study at a university medical center determined whether patients randomized to a mobility protocol received more physical therapy than patients in usual care. An ICU mobility team consisting of a critical care nurse, a nursing assistant, and a physical therapist initiated the mobility protocol within 48 hours of initiating mechanical ventilation. The mobility protocol patients received at least one more physical therapy session than the usual care group (80% vs. 47%, p≤0.001). Patients in the mobility protocol group were out of bed earlier (5 vs. 11 days, p≤0.001), had therapy started more often in the ICU (91% vs. 13%, p≤0.001), and had complication rates similar to the usual care group. The protocol group had ICU length of stay of 5.5 days (versus 6.9 days in the usual care group; p=0.025), and hospital length of stay of 11.2 days (versus 14.5 in the usual care group; p=0.006). No cost difference was found between groups (Morris 2008).

Pharmacists can play a key role in every step of the ABCDEF bundle through providing staff education and ensuring performance and discussion on rounds of each individual component. Pharmacists can ensure that pain is assessed for, prevented, and treated with the best pharmacologic agent. Ensuring the performance, coordination, and discussion on rounds of SATs and SBTs, in addition to providing evidence-based recommendations for the choice of analgesia and sedation, are important roles that pharmacists can champion. Providing education, confirming or appropriately assessing and documenting, and selecting appropriate nonpharmacologic or pharmacologic therapy for delirium are other key roles of pharmacists. Pharmacists can appropriately screen and recommend physical therapy consultation to initiate early mobility and exercise. Finally, pharmacists can answer any questions the family may have with respect to the ABCDEF bundle.

CONCLUSION

Pain should be routinely monitored in all ICU patients using an objective, reliable tool. Goal-directed delivery of sedatives is best accomplished using validated sedation scales such as the RASS and SAS to enable the medical team to agree on a target sedation level for each individual patient and titrate medications to achieve this goal. All adult patients should be regularly monitored for delirium using either the CAM-ICU or the ICDSC. The ABCDEF is an evidence-based way to coordinate care among several disciplines, including pharmacists, resulting in decreased sedation exposure, duration of mechanical ventilation, and ICU-acquired delirium and weakness. Several intervention studies, many of which highlight the important role of pharmacists, have implemented various components of the ABCDEF bundle.

Practice Points

In determining the optimal means for monitoring and developing pathways for PAD, practitioners should consider the following:

- **Pain should be routinely monitored in all ICU patients using an objective, reliable tool. Self-reporting of pain is the gold standard. If the patient cannot self-report, the PAD guidelines recommend the CPOT or BPS to assess pain.**
- **Goal-directed delivery of sedatives is best accomplished using the RASS or SAS to enable the medical team to agree on a target sedation level for each individual patient and titrate all medications used for analgosedation or sedation to achieve this goal.**
- **All adult patients should be regularly monitored for delirium using either the CAM-ICU or the ICDSC. Hypoactive delirium is often undiagnosed if a validated tool is not used for assessing delirium.**
- **The ABCDEF is an evidence-based way to coordinate interdisciplinary care including pharmacists, resulting in decreased sedation exposure, duration of mechanical ventilation, and ICU-acquired delirium and weakness. Several interventional studies have implemented various components of the ABCDEF bundle. Many of these studies highlight the important role of pharmacists in implementing and maintaining compliance with these interventions.**

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Self-Assessment Questions

Questions 21–25 pertain to the following case.

T.G. is a 70-year-old man with a carcinoid tumor who is admitted to the surgical ICU after a subtotal colectomy. He is currently mechanically ventilated and receiving propofol at 20 mcg/kg/minute and fentanyl at 50 mcg/hour. His other drugs include famotidine 20 mg nasogastrically daily, enoxaparin 40 mg subcutaneously daily, loratadine 10 mg nasogastrically daily, piperacillin/tazobactam 3.375 g intravenously every 8 hours, and vancomycin 1500 mg intravenously every 24 hours. T.G. is grimacing, pulling at his endotracheal tube, thrashing, and showing resistance to passive movements and is asynchronous with the ventilator. He is very aggressive to the staff and is trying to pull out his endotracheal tube. T.G.'s Richmond Agitation-Sedation Scale (RASS) score has fluctuated over the past 24 hours from -3 to +3. At baseline, he volunteers at the gift shop in the hospital and walks his dog 2 miles every day. He makes three errors during SAVE A HAART. T.G. answers three of the four questions in feature 4 correctly and does not correctly complete the full command.

21. Which one of the following best represents T.G.'s Critical-Care Pain Observation Tool (CPOT) score?

    A. 5
    B. 4
    C. 6
    D. 7

22. Which one of the following best represents T.G.'s current RASS score?

    A. 0
    B. -1
    C. +3
    D. -4

23. Which one of the following will most likely result in T.G. meeting the criteria for feature 2 (inattention) of the confusion assessment method for the ICU (CAM-ICU)?

    A. He makes three errors during SAVE A HAART.
    B. He answers only three of the four questions correctly and does not correctly complete the full command.
    C. His RASS is -1.
    D. He has a fluctuating mental status.

24. Which one of the following will most likely result in T.G. meeting the criteria for feature 4 (disorganized thinking) of the CAM-ICU?

    A. His RASS is 0.
    B. He makes three errors during SAVE A HAART.
    C. He has fluctuating mental status.
    D. He answers only three of the four questions correctly and cannot complete the full command.

25. Which one of the following best describes T.G.'s CAM-ICU?

    A. CAM-ICU negative
    B. CAM-ICU positive
    C. Unable to assess
    D. Subsyndromal delirium

Questions 26–30 pertain to the following case.

K.P. is a 37-year-old man who presents to the ED after a motor vehicle crash in which he was unrestrained. He has bilateral acetabular and right ankle fractures and a grade 3 splenic laceration. He is mechanically ventilated in the trauma unit and receiving propofol at 40 mcg/kg/minute and fentanyl at 200 mcg/hour. K.P.'s current drugs include famotidine 20 mg nasogastrically twice daily, enoxaparin 40 mg subcutaneously daily, and senna 8.8 mg nasogastrically daily. He is receiving enteral nutrition at 40 mL/hour. K.P.'s face is relaxed, he is not moving his upper limbs, and he is coughing but tolerating the ventilator most of the time. He currently makes eye contact to voice greater than 10 seconds. The patient's RASS has ranged from +1 to -4 over the past 24 hours. At baseline, the patient mows his lawn at home regularly and is his son's soccer coach. He makes one error when the nurse uses the picture cards to perform the visual attention test. K.P. answers three of the four questions in feature 4 correctly and correctly completes the full command.

26. Which one of the following best represents K.P.'s Behavioral Pain Scale score?

    A. 4
    B. 5
    C. 6
    D. 7

27. Which one of the following best represents K.P.'s current RASS score?

    A. 0
    B. -1
    C. -3
    D. -4

28. Which one of the following will most likely result in K.P. meeting the criteria for feature 1 (acute fluctuation in mental status)?

    A. He makes one error during the picture cards.
    B. He answers three of the four questions in feature 4 correctly and correctly completes the full command.
    C. His RASS is 2.
    D. His RASS has ranged from +1 to -4 over the past 24 hours.

29. Which one of the following will most likely result in K.P. not meeting the criteria for feature 2 (inattention)?

    A. His RASS is -1.
    B. He makes one error during the picture cards.
    C. He answers only three of the four questions correctly and completes the full command.
    D. His RASS has ranged from +1 to -4 over the past 24 hours.

30. Which one of the following best represents K.P.'s CAM-ICU assessment?

    A. CAM-ICU negative
    B. CAM-ICU positive
    C. Unable to assess
    D. Subsyndromal delirium

Questions 31–34 pertain to the following case.

L.G. is a 56-year-old woman who is transferred from an outside facility with acute hypoxic respiratory failure secondary to community-acquired pneumonia. She arrives on the following mechanical ventilation settings: volume control, Fio_2 60%, positive end-expiratory pressure (PEEP) 7 mm H_2O, respiratory rate 15 breaths/minute, and tidal volume (TV) 340 mL with Sao_2 92%. L.G. is sedated with propofol 10 mcg/kg/minute and fentanyl 25 mcg/hour. Her drugs include famotidine 20 mg nasogastrically twice daily, enoxaparin 40 mg subcutaneously daily, azithromycin 500 mg nasogastrically every 24 hours, and ceftriaxone 1 g intravenously daily. L.G. is difficult to arouse but awakens to the nurse's voice. She follows simple commands but quickly drifts back to sleep. The patient makes three mistakes on the letter A's when the nurse performs the SAVE A HAART. The patient knows her name, knows that she is in the hospital, and knows the day of the week. She also recognizes her nurse. The nurse asks L.G. if she is having any hallucinations. Although L.G. replies that the Easter bunny popped into her room twice this morning to offer her chocolate, she is not hallucinating at other times. The patient is not hyperactive or a danger to the staff. L.G.'s behavior is appropriate, and she slept 5 hours last night without frequent awakenings.

31. Which one of the following best represents L.G.'s current Sedation-Agitation Scale (SAS) score?

    A. 4
    B. 5
    C. 3
    D. 6

32. Which one of the following best represents the results of L.G.'s Intensive Care Delirium Screening Checklist assessment?

    A. No delirium
    B. Delirium
    C. Unable to assess
    D. Subsyndromal delirium

33. Which one of the following best explains why L.G. is not an appropriate candidate for a spontaneous breathing trial (SBT)?

    A. Her Sao_2 is only 92%.
    B. Her Fio_2 is 60%.
    C. Her PEEP is 7 mm H_2O.
    D. She has subsyndromal delirium.

34. Which one of the following best explains why L.G. is an appropriate candidate for physical therapy?

    A. Her SAS is 2.
    B. Her Fio_2 is 60%.
    C. She has delirium.
    D. She slept 5 hours last night.

35. In the ABC Study, the SAT coordinated with the SBT (ABC group) had a 44% mortality rate at 1 year versus the SBT plus sedation by usual care, which had a 58% mortality rate at one year. What is the number needed to treat with the ABC protocol to save one life?

    A. 5
    B. 7
    C. 10
    D. 12

Questions 36–40 pertain to the following case.

S.V. is a 70-year-old woman who is admitted to the ICU with acute hypercarbic respiratory failure secondary to a chronic obstructive pulmonary disease exacerbation. She is mechanically ventilated and receiving midazolam at 1 mg/hour and fentanyl at 200 mcg/hour this morning. S.V. has the following mechanical ventilation settings: volume control, PEEP 7 mm H_2O, FIO_2 50%, and TV 400 mL with Sao_2 93%. Her current drugs include famotidine 20 mg nasogastrically twice daily, enoxaparin 40 mg subcutaneously daily, azithromycin 500 mg nasogastrically every 24 hours, prednisone 40 mg nasogastrically daily, and albuterol/ipratropium nebulizers every 6 hours. At baseline, S.V. works in her garden, sings in her church choir, and babysits her grandchildren regularly. The patient is grimacing; her movements are slow and cautious; she has no resistance to passive movements; and she is tolerating the ventilator. She currently does not respond to voice but does respond to physical stimulation. Her RASS has ranged from -4 to +2 over the past 24 hours. The patient's goal RASS is 0. When you assess S.V. for inattention using SAVE A HAART, she misses four of the letter A's. She answers none of the questions in feature 4 and does not complete the full command.

36. Which one of the following best represents S.V.'s CPOT score?

    A. 1
    B. 2
    C. 3
    D. 4

37. Which one of the following best represents S.V.'s current RASS score?

    A. 1
    B. -1
    C. +3
    D. -4

38. Which one of the following is the best interpretation of S.V.'s CAM-ICU assessment?

    A. CAM-ICU negative
    B. CAM-ICU positive
    C. Unable to assess
    D. Subsyndromal delirium

39. Because S.V. has not been given a SAT, you educate your team about the ABC Study. The resident on your team looks at the study and notes that in the SAT coordinated with the SBT (ABC group), the self-extubation requiring reintubation within 48 hours of extubation rate was 3% versus the SBT plus sedation by usual care group which had a rate of 2%. What is the number needed to harm with the ABC protocol resulting in one self-extubation requiring reintubation within 48 hours of extubation?

    A. 50
    B. 75
    C. 100
    D. 125

40. While on interprofessional rounds, you notice that S.V. is not at her goal RASS and has not had the SAT or SBT this morning. Which one of the following best supports your recommendation for S.V. to have a SAT/SBT?

    A. Her RASS is not at goal.
    B. Performing the SAT coordinated with the SBT resulted in fewer days on the ventilator, fewer days in the ICU, and a 14% reduction in mortality in one multicenter, prospective study.
    C. She has delirium.
    D. Her FIO_2 is 50%.

Learner Chapter Evaluation: Pain, Agitation, and Delirium Monitoring/ Pathway Development.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. The content of the chapter met my educational needs.
21. The content of the chapter satisfied my expectations.
22. The author presented the chapter content effectively.
23. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
24. The content of the chapter was objective and balanced.
25. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
26. The content of the chapter was useful to me.
27. The teaching and learning methods used in the chapter were effective.
28. The active learning methods used in the chapter were effective.
29. The learning assessment activities used in the chapter were effective.
30. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

31. Apply the different pain monitoring tools used in critically ill patients.
32. Demonstrate how to use the RASS and SAS for monitoring a patient's level of consciousness.
33. Apply validated tools for monitoring delirium.
34. Evaluate the benefits and the components of the ABCDEF bundle in critically ill patients.
35. Justify the role of the interprofessional team, including the pharmacist, in implementing the ABCDEF bundle.
36. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
37. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 38–40 apply to the entire learning module.

38. How long did it take you to read the instructional materials in this module?
39. How long did it take you to read and answer the assessment questions in this module?
40. Please provide any additional comments you may have regarding this module:

Support and Prevention III

Support and Prevention I Panel

Series Editors:

Bradley A. Boucher, Pharm.D., FCCP, FNAP, MCCM, BCPS
Professor of Clinical Pharmacy
Associate Dean for Strategic Initiatives and Operations
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Curtis E. Haas, Pharm.D., FCCP
Director of Pharmacy
University of Rochester Medical Center
Rochester, New York

Faculty Panel Chair:

Amy L. Dzierba, Pharm.D., BCPS, BCCCP, FCCM
Critical Care Pharmacist, Medical Intensive Care Unit
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

Prophylaxis of Stress Ulcer and Deep Vein Thrombosis

Authors

Mitchell S. Buckley, Pharm.D., FCCP, FASHP, FCCM, BCCCP
Clinical Pharmacy Specialist, Critical Care
Department of Pharmacy
Banner-University Medical Center Phoenix
Phoenix, Arizona

Justin Muir, Pharm.D.
Clinical Pharmacy Manager, Medical Intensive Care Unit
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

Reviewers

Jill A. Rebuck, Pharm.D., MBA, FCCP, FCCM, BCPS
Director, Clinical Pharmacy Services
Department of Pharmacy
Penn State Hershey, Milton S. Hershey Medical Center
Hershey, Pennsylvania

Manish Patel, Pharm.D., BCPS
Clinical Pharmacist
Department of Pharmacy
Summerlin Hospital Medical Center
Las Vegas, Nevada

Perioperative Management: Cardiac and Vascular Surgery

Authors

James C. Coons, Pharm.D., BCPS-AQ Cardiology
Associate Professor
Department of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Clinical Specialist, Cardiology
Department of Pharmacy
UPMC Presbyterian Hospital
Pittsburgh, Pennsylvania

Matthew R. Wanek, Pharm.D., BCPS, BCCCP
Cardiovascular ICU Clinical Specialist
PGY2 Critical Care Residency Program Director
Department of Pharmacy
Cleveland Clinic
Cleveland, Ohio

Reviewers

William J. Peppard, Pharm.D., BCPS
Surgical ICU Pharmacist
Department of Pharmacy
Froedtert Hospital
Assistant Professor
Department of Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin

Julianna W. Gachoya, Pharm.D., BCPS, MBA-MHA
Clinical Coordinator
Department of Pharmacy
Medstar Washington Hospital Center
Washington, District of Columbia

Peri-operative Management: ransplantation and Neurosurgery

Heather Personett, Pharm.D., BCPS, BCCCP
Clinical Pharmacist, Critical Care and Transplantation
Department of Pharmacy
Mayo Clinic
Assistant Professor of Pharmacy
Mayo Clinic College of Medicine
Rochester, Minnesota

Hira Shafeeq, Pharm.D., BCPS
Assistant Professor
Clinical Health Professions
St. John's University
Queens, New York

Reviewers

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Christine A. Lesch, Pharm.D., BCPS

Clinical Pharmacy Manager, Critical Care
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Medical Center
New York, New York

Shawn E. Fellows, Pharm.D., BCPS

Assistant Professor of Pharmacy Practice
Wegmans School of Pharmacy-St. John Fisher College
Rochester, New York

Russell Dixon, Pharm.D., BCCCP

Trauma, Surgical, and Neurologic Critical Care, Clinical Pharmacist
Oklahoma University and Southwestern Oklahoma State University Adjunct Faculty
Department of Pharmacy
St. John Medical Center
Tulsa, Oklahoma

H. Gwen Bartlett, Pharm.D., BCPS

Assistant Professor of Pharmacy Practice
School of Pharmacy
Husson University
Bangor, Maine

Emilie Karpiuk, Pharm D., BCPS

Oncology Pharmacist
Department of Pharmacy
Froedtert Hospital
Milwaukee, Wisconsin

Jeffrey T. Sherer, Pharm.D., MPH, BCPS

Clinical Associate Professor
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

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Prophylaxis of Stress Ulcer and Deep Venous Thrombosis

By Mitchell S. Buckley, Pharm.D., FCCP, FASHP, FCCM, BCCCP; and Justin Muir, Pharm.D.

Reviewed by Jill A. Rebuck, Pharm.D., MBA, FCCP, FCCM, BCPS; and Manish Patel, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Analyze major risk factors for clinically significant GI bleeding associated with stress-related mucosal disease.
2. Develop an evidence-based strategy for managing stress ulcer prophylaxis in the ICU setting.
3. Analyze major risk factors for venous thromboembolism (VTE) in the critically ill population.
4. Design an evidence-based strategy for VTE prophylaxis in the ICU.

ABBREVIATIONS IN THIS CHAPTER

ACCP	American College of Chest Physicians
CDI	*Clostridium difficile* infection
DVT	Deep venous thrombosis
GCS	Graduated compression stockings
GIB	GI bleeding
HIT	Heparin-induced thrombocytopenia
H_2RA	Histamine-2 receptor antagonist
IPC	Intermittent pneumatic compression
IVC	Inferior vena cava
LMWH	Low-molecular-weight heparin
PPI	Proton pump inhibitor
SRMD	Stress-related mucosal disease
SUP	Stress ulcer prophylaxis
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Table of other common abbreviations.

INTRODUCTION

Critically ill patients are often at risk of acquiring iatrogenic complications. Two common, yet preventable complications in ICU patients are GI bleeding (GIB) related to stress-related mucosal disease (SRMD); and venous thromboembolism (VTE). Although nonpharmacologic measures are often used to prevent these ICU-acquired disease state processes, most critically ill patients in an ICU are prescribed prophylactic drug therapy. Acid-suppressive agents are the most commonly prescribed off-label drugs in the ICU. Both stress ulcer prophylaxis (SUP) and anticoagulation agents are effective in reducing the risk that critically ill patients will develop GIB associated with SRMD and VTE, respectively. However, these therapies are associated with harmful complications. Health care professionals, including clinical pharmacists, continue to struggle to identify the patients most likely to benefit from drug therapy prophylaxis as well as the optimal agent. This chapter discusses SUP and VTE prophylaxis in the ICU, the patients at a high risk of these complications, and how to maximize drug efficacy, minimize potential adverse drug events, and avoid unnecessary medication costs.

STRESS-RELATED MUCOSAL DISEASE

Definition

Stress-related mucosal disease is an erosive process of the gastroduodenum that occurs in patients with altered physiologic demands from an acute insult (e.g., trauma, surgery, burns, sepsis) (Kleiman 1988). Stress-related mucosal disease is a different disease entity from peptic ulcer disease

with a different pathogenesis. Peptic ulcer disease is a tear in the gastric, esophageal, or duodenal mucosal lining commonly caused by medications and bacteria (*Helicobacter pylori*). Peptic ulcers typically develop as a result of the corrosive action of pepsin and hydrochloric acid, whereas SRMD is primarily associated with splanchnic hypoperfusion. However, SRMD superficial erosive lesions developing in the GI epithelium may progress to gastric ulcers.

Given the diffuse nature of these lesions, endoscopic therapy (e.g., injection methods, cautery, mechanical modalities) may not be a feasible management strategy. As the clinical status and severity of illness of the ICU patient improves, most of these GI lesions may resolve without intervention. However, critically ill patients may experience GIB as a result of SRMD during their ICU stay. Upper GIB complications have been characterized as either overt or clinically significant bleeding, although the specific definition criteria may vary among studies (Box 1-1).

Box 1-1. Upper GI Bleeding Definitions Associated with Stress-Related Mucosal Disease

Overt (including any of the following criteria):

- Hematemesis
- Gross blood or "coffee ground"–appearing substances from nasogastric aspirate
- Hematochezia
- Melena

Clinically Significant (the presence of overt bleeding with any of the following criteria within 24 hr of event):

- SBP or DBP decrease ≥ 20 mm Hg
- HR increase > 20 beats/minute
- Hgb decrease of at least 2 g/dL and transfusion of 2 units of packed red blood cells, after which Hgb does not increase by a value defined as the number of units transfused minus 2 g/dL

DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Epidemiology

Stress-related mucosal disease is common in critically ill patients and develops rapidly after ICU admission. Endoscopic evidence of asymptomatic mucosal damage has been reported in over 74% of mechanically ventilated patients. Despite the high incidence of mucosal damage in ICU patients, only a small portion of these patients progress to clinically significant GIB. In a landmark, multicenter, prospective trial, the rate of clinically significant GIB was 1.5% among 2252 patients (Cook 1994). This is consistent with another epidemiologic study evaluating critically ill patients over the past decade, which showed a clinically significant GIB rate of 4.4% (MacLaren 2014b). Recently, another large study involving 1034 patients among 97 ICUs in 11 countries found the incidence of clinically significant GIB to be 2.6% (Krag 2015).

Given the paradigm shift over the past decade of early resuscitation strategies in ICU patients with possible splanchnic hypoperfusion, the incidence of these patients experiencing clinically significant GIB has decreased. This may explain the higher rates in an era reflective of a lack of early recognition and treatment compared with today. The onset of stress ulceration may begin to develop within 24 hours of ICU admission. Overt GIB caused by stress ulceration is associated with increased mortality and morbidity. The length of stay in the ICU may be prolonged, and the risk of death increases.

Pathophysiology

The pathogenesis of GIB attributed to SRMD is multifactorial. The primary pathway in critically ill patients involves decreased gastric blood flow and mucosal ischemia (Plummer 2014). Proinflammatory cytokines, often present in ICU patients as a response to acute illness, may induce hypotension. In addition, ICU patients often experience systemic hypotension, increased catecholamine release, increased vasoconstriction, and hypovolemia leading to hypoperfusion to the GI mucosal cells. Of interest, splanchnic hypoperfusion may be present despite systemic hemodynamic stability in the critically ill population. Furthermore, mechanical ventilation may adversely affect mesenteric blood flow, although

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Role of enteral nutrition for SUP
- General knowledge regarding the impact of acid-suppressive therapy as SUP in the general ward population
- General knowledge of the coagulation cascade
- General knowledge of the activity of anticoagulants and antiplatelet agents

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Hurt RT, Frazier TH, McClave SA, et al. Stress ulcer prophylaxis in intensive care unit patients and the role of enteral nutrition. J Parenter Enteral Nutr 2012;36:721-31.
- Grube RR, May DB. Stress ulcer prophylaxis in hospitalized patients not in intensive care units. Am J Health Syst Pharm 2007;64:1396-400.
- American College of Chest Physicians (ACCP). Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. Chest 2012;141(2 suppl).

this remains controversial. Ventilation strategies with high tidal volumes or positive end-expiratory pressure (PEEP) have been associated with decreased venous return and cardiac output. Activation of the renin-angiotensin-aldosterone system and catecholamine release may attribute to PEEP. These mechanical ventilation–induced physiologic changes lead to splanchnic hypoperfusion, yet their role in contributing to GIB in the ICU has not been validated.

Additional factors may be involved in stress-related mucosal GIB. After direct mucosal damage and mesenteric ischemia, several physiologic changes may disrupt processes that maintain GI mucosal integrity. Reduced bicarbonate production may lead to decreased intramucosal pH; this increased acidic environment may propagate ulceration. Intestinal acid reflux into the stomach (i.e., acid back-diffusion) and decreased GI motility may increase the risk of GIB (Plummer 2014). Acid and bile salts may also play an important role. Although splanchnic hypoperfusion is the most commonly accepted pathway, this process may be multifactorial, and despite common misconceptions, gastric acid production is not a primary cause of SRMD-associated GIB.

Risk Factors for Stress Ulcer-Related GIB

Risk factors for developing stress-related mucosal GIB remain a source of debate. Acid-suppressive agents are not benign therapies; their associated complications raise significant concerns. To prevent GIB in a safe and effective manner, optimal SUP should involve appropriate use in the ICU patients at highest risk, while minimizing associated adverse drug events. The risk of GIB associated with SRMD increases with the number of risk factors present. Potential predisposing factors include respiratory failure, coagulopathy, hepatic failure, renal dysfunction, thermal injury, major surgery, organ transplantation, hypotension, and sepsis.

The Canadian Critical Care Trials Group enrolled more than 2000 patients in a landmark prospective, multicenter clinical trial to investigate potential risk factors for clinically significant GIB associated with stress ulcers. Clinically significant GIB occurred in 1.5% of all patients (95% CI, 1.0%–2.0%), 69.7% of whom died while receiving SUP. Although several variables were identified as significant risk factors for stress-related GIB, only two independent risk factors were identified on multiple regression analysis. These occurred in critically ill patients (predominantly cardiovascular surgery) requiring mechanical ventilation for more than 48 hours (OR 15.6) and those who experienced a coagulopathy (OR 4.3). The incidence of clinically significant GIB in patients considered high risk (with either respiratory failure or coagulopathy; n=847) compared with low risk (n=1405) was 3.7% (95% CI, 2.5%–5.2%) and 0.1% (95% CI, 0.02%–0.5%), respectively. Furthermore, around 80% of low-risk patients received no pharmacologic prophylaxis. Given these findings, the authors recommend against using prophylaxis in "low-risk" patients while limiting SUP to patients with 48 hours or greater mechanical ventilation and/or coagulopathy (Box 1-2) (Cook 1994). However, clinicians should recognize that most of the study population consisted of cardiovascular surgery patients, who had a relatively low mortality rate (9.7%). Therefore, the clinical utility of these recommendations may not be reflective of other ICU patients.

The Canadian Critical Care Trials Group further evaluated risk factors for clinically significant GIB, specifically in a cohort of 1200 ICU patients requiring mechanical ventilation for 48 hours or more. The many risk factors evaluated included sex, primary diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, multiple organ dysfunction score, Glasgow Coma Scale score, serum creatinine, absolute platelet count, inotropic agent use, antibiotic administration, and other comorbidities. Similar to the earlier study by the same investigators, univariate regression analysis found several variables associated with an increased risk of GIB. However, the only independent risk factor in multivariable regression analysis was the maximum serum creatinine (RR 1.16; 95% CI, 1.02–1.32; p=0.023). In addition, enteral nutrition significantly reduced the risk of GIB (RR 0.30; 95% CI, 0.13–0.67; p=0.004) (Cook 1999). Therefore, this study suggested that renal failure predisposes critically ill patients to developing stress-related GIB.

A large pharmacoepidemiologic cohort study involving more than 35,000 adult ICU patients among 71 hospitals investigated risk factors for GIB. Subjects were identified using the International Classification of Diseases, Ninth Revision codes for GIB as a secondary diagnosis (i.e., occurring during admission, although not present on initial hospital presentation). Variables associated with an increased risk

Box 1-2. Risk Factors for Clinically Significant GI Bleeding

- Respiratory failure requiring mechanical ventilation for ≥ 48 hr[a]
- Coagulopathy (Plt < 50,000/mm^3, INR > 1.5, or PTT 2-fold higher than control)[a]
- Hypotension
- Sepsis
- Hepatic failure
- Renal dysfunction
- Renal replacement therapy
- Enteral feeding (protective factor)
- Organ transplantation
- Glucocorticoid use (> 200 mg of hydrocortisone or equivalent per day)
- Anticoagulant drug therapy
- Chronic obstructive pulmonary disease
- Thermal injury
- Neurologic injury
- Myocardial infarction

[a]Greatest level of evidence for stress ulcer prophylaxis.

Information from Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 1994;330:377-81.

Patient Care Scenario

A man is admitted to the ICU for health care–associated pneumonia and septic shock requiring mechanical ventilation. Eight days after admission, he is still in the ICU; however, he is now clinically stable and no longer requires vasoactive support. His only major comorbidity is chronic obstructive pulmonary disease with no acute exacerbation, and he has no laboratory abnormalities. The patient has been extubated, but he requires bilevel positive airway pressure (BiPAP). Does this patient still require SUP?

ANSWER

The clinical conundrum facing many providers is determining the optimal duration for SUP or when to discontinue therapy in ICU patients. Mechanical ventilation is a well-known independent risk factor for SRMD. Some modes of invasive mechanical ventilation have decreased cardiac output, thus potentially contributing to splanchnic hypoperfusion. However, the clinical significance of this remains controversial.

BiPAP is a noninvasive form of mechanical pressure support ventilation. This mode can be used in ICU as well as non-ICU patients and in outpatients. Theoretically, this mode of ventilation may cause increased intrathoracic pressure, leading to decreased venous return to the heart, resulting in lower cardiac output.

Although a clinician may challenge that this patient still requires ventilator support, it is important to recognize the patient is no longer considered "critically ill." Therefore, SUP in this patient should be discontinued.

1. Jakob SM. The effects of mechanical ventilation on hepato-splanchnic perfusion. Curr Opin Crit Care 2010;16:165-8.
2. Masip J. Non-invasive ventilation. Heart Fail Rev 2007;12:119-24.

of GIB on multivariate analyses included age older than 50 years, male sex, acute respiratory failure, sepsis, shock, acute kidney injury, acute and chronic liver failure, neurologic injury, myocardial infarction, and coagulopathy. Most of these risk factors are consistent with previous findings. However, some variables previously shown to increase the risk of GIB were not adequately represented in this cohort study (e.g., transplantation, thermal injury, major surgery or trauma, corticosteroids, thrombocytopenia) (MacLaren 2014b).

Another recent trial involving over 1000 patients among 97 ICUs in 11 countries also tried to determine the risk factors resulting in clinically significant GIB. The risk factors associated with clinically significant GIB included higher severity of illness scores (Simplified Acute Physiologic Score and sepsis-related organ failure assessment), liver cirrhosis or elevated bilirubin greater than 1.9 mg/dL, and renal replacement therapy (Krag 2015). Unlike other trials, this study failed to show mechanical ventilation as a risk factor for GIB when defined as invasive mechanical ventilation present on ICU admission.

SUP OPTIONS

Histamine-2 Receptor Antagonists

The histamine-2 receptor antagonists (H_2RAs) are commonly prescribed acid-suppressive agents that decrease gastric acid secretion through reversible, competitive inhibition of the histamine-2 receptor on the basolateral membrane of the parietal cell. These agents vary in potency from famotidine (most potent) to ranitidine (intermediate) to cimetidine (least potent). The only H_2RA with FDA-approved labeling for SUP is cimetidine, administered as a continuous infusion. Tachyphylaxis can develop within 72 hours of initiating H_2RA therapy (Mohebbi 2009). The histamine-2 substrate is just one pathway to stimulate gastric acid secretion on the parietal cell. Alternative pathways (e.g., gastrin, acetylcholine) can be upregulated in response to the use of H_2RAs, leading to a decline in gastric pH; this explains tolerance and rebound related to H_2RAs. Furthermore, these agents should be renally dosed.

The adverse effect profile of H_2RAs generally includes diarrhea, headache, drowsiness, fatigue, and constipation. Cimetidine has drug-specific adverse events affecting several organs and drug-drug interactions. For these reasons, as well as concerns related to 24-hour continuous intravenous infusion therapy, cimetidine is rarely chosen for SUP in clinical practice.

Histamine-2 receptor antagonist–induced thrombocytopenia remains controversial. Two possible mechanisms have been proposed. The first hypothesis involves direct bone marrow suppression through DNA synthesis inhibition, whereas less likely is an autoimmune response with platelet antibodies developing after H_2RA exposure. Although the association between H_2RA use and thrombocytopenia in the ICU is assumed to be well established, the evidence supporting this connection is limited to case reports (Wade 2002). Among the 29 case reports summarized in this review, over 90% of patients had at least one other independent risk factor for thrombocytopenia, and 69% of the cases involved cimetidine. The data supporting claims that drug-induced thrombocytopenia is caused by H_2RAs are weak and may not warrant changing H_2RA therapy to an alternative option.

Proton Pump Inhibitors

The proton pump inhibitors (PPIs) are commonly prescribed off-label agents that result in profound irreversible acid suppression. These medications are prodrugs requiring an acidic environment (i.e., protonation) to occur in the secretory

canalicular space of the stimulated parietal cell (Shin 2008). Because the acidic environment of the stomach would render the parent compound unstable, oral PPI formulations are enteric coated to allow passage through the stomach into the duodenum, where the coating dissolves. After activation of the prodrug in the duodenum, PPIs bind to the cysteine site with the hydrogen-potassium-adenosinetriphosphatase enzyme, resulting in inhibition of the final step of gastric acid secretion. Proton pump inhibitors can only inhibit gastric acid pumps, which are activated during the short half-life (i.e., 90 minutes) after administration. Despite the short half-life of the drug, the duration of action may be up to 48 hours because of irreversible binding to the proton pump.

Several adverse drug events are associated with PPI use; common ones are related to GI complications (e.g., diarrhea, nausea and vomiting, abdominal pain), although headaches and rashes may also occur. Proton pump inhibitors may modify intestinal absorption of magnesium, and chronic use (beyond 3 months) may increase the risk of hypomagnesemia (Sheen 2011). Acute interstitial nephritis is another concern with PPI use. The risk of bone fractures may increase with long-term PPI use. Moreover, vitamin B_{12} deficiencies have occurred with chronic use. A significant drug-drug interaction between omeprazole and clopidogrel has led to adverse cardiovascular events; the FDA issued a warning to avoid concomitant therapy. The platelet anti-aggregation effect of clopidogrel may be diminished with omeprazole. Because these observations have not been corroborated with pantoprazole, it remains unclear whether this phenomenon is a drug class effect or agent-specific.

OPTIMAL SUP

The optimal choice of pharmacotherapy for SUP is controversial. One recent meta-analysis corroborated that SUP significantly reduced clinically significant GIB compared with placebo or no prophylaxis in a neurocritical care population (Liu 2015). However, this investigation did not directly compare H_2RAs and PPIs, the two agents most commonly used in the ICU. Proton pump inhibitors are superior to H_2RAs in effectively increasing gastric pH and maintaining acid suppression. However, the superior acid suppression with PPIs does not significantly reduce the rate of SRMD-related GIB in ICU patients. Clinicians are challenged not only in identifying the most effective agent, but also in balancing the potential adverse drug events (which may have prolonged safety concerns) and differences in treatment costs. Furthermore, because the optimal duration of use in the ICU is controversial, there is significant variability in clinical practice (Daley 2004; Lam 1999).

Clinical Practice Guideline Recommendations

Several clinical practice guidelines on SUP have been published (Table 1-1). In 1999, the American Society of Health-System Pharmacists published the first evidence-based guideline on SUP (ASHP 1999). However, the clinical utility of this guideline is obsolete and most of the recommendations are outdated.

The 2008 Eastern Association for the Surgery of Trauma guidelines give the highest level of recommendation for initiation of prophylaxis in mechanically ventilated patients, or in ICU patients with coagulopathy, traumatic brain injury, or major thermal injury (Guillamondegui 2008). Moderate level of recommendation is given to prophylaxis in patients with multiple trauma, sepsis, and acute renal failure. Other risk factors (e.g., high-dose corticosteroids) were suggested on the basis of expert opinion. Cytoprotective agents, H_2RAs, and PPIs were equally recommended as preferred agents, whereas prophylaxis with antacids was not recommended. The authors also recommended continued use of prophylaxis as long as risk factors are present, the patient remains in the ICU, or until a minimum of 1 week after the onset of critical illness. Because these recommendations were not supported by a robust methodology that graded the available evidence and may be more reflective of expert opinion, they are not strictly adhered to in clinical practice today.

The 2012 Surviving Sepsis Campaign published by the Society of Critical Care Medicine also provided recommendations on SUP (Dellinger 2013). Prophylaxis with H_2RAs and PPIs was given the highest recommendation in patients with

Table 1-1. Stress Ulcer Prophylaxis Clinical Guideline Summary

Guideline (Year Published)	Preferred Agent
Eastern Association for the Surgery of Trauma (2008)	• Cytoprotective agents, H_2RAs, or PPIs may be used • Antacids are not recommended
Surviving Sepsis Campaign (2012)	• H_2RAs or PPIs may be used in patients with severe sepsis/septic shock in the ICU • PPIs are preferred
Danish Society of Intensive Care Medicine and Danish Society of Anaesthesiology and Intensive Care Medicine (2014)	PPIs are preferred

H_2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.

Information from Guillamondegui OD, Gunter OL, Bonadies JA, et al. Practice Management Guidelines for Stress Ulcer Prophylaxis 2008. Available at www.east.org. Accessed September 25, 2015; Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637; and Madsen KR, Lorentzen K, Clausen N, et al. Guideline for stress ulcer prophylaxis in the intensive care unit. Dan Med J 2014;61:C4811.

severe sepsis/septic shock and bleeding risk factors. These guidelines further suggest PPIs be used as first-line therapy, but this was a weak recommendation (i.e., 2D) based on a very low quality of evidence. Recommended duration of use was provided, but it was stated that patients without risk factors should not receive prophylaxis.

The Danish Society of Intensive Care Medicine and the Danish Society of Anaesthesiology and Intensive Care Medicine recently published clinical practice guidelines (Madsen 2014). Rather than recommend, this document "suggests" PPIs as the preferred prophylactic choice, according to a weak recommendation with low-quality evidence. No recommendations were provided for duration of use or risk factor stratification.

Comparative Safety and Efficacy Analysis of SUP Regimens

The superior efficacy of one acid-suppressive agent over another in reducing the risk of clinically significant GIB remains unresolved. The heterogeneity among trials and discordant results pose a challenge in apply these findings to clinical practice. Significant variability among trials included the drugs used, dosing strategy, definition of clinically significant GIB, endoscopic GIB diagnostic confirmation, ICU patient population, risk factor stratification, and study design.

Several meta-analyses have tried to identify the optimal agent in reducing the risk of clinically significant GIB without increasing the risk of pneumonia (Table 1-2). Only four meta-analyses compared bleeding rates between PPIs and H_2RAs (Alhazzani 2013a; Barkun 2012; Lin 2010; Pongprasobchai 2009). Most of these analyses showed the superiority of PPIs to H_2RAs in preventing clinically significant GIB. Although it appears that PPIs have better efficacy in reducing the risk of GIB than H_2RAs, a large pharmacoepidemiologic cohort study found PPIs to be less effective (MacLaren 2014b). The GIB rates in the PPI and H_2RA groups were 5.9% and 2.1% ($p<0.001$), respectively.

Enteral nutrition as a viable SUP agent without concomitant antisecretory therapy has been debated for decades. Enteral nutrition maintains the integrity of the GI mucosa by increasing splanchnic blood flow, thereby serving as a viable option for SUP (Hurt 2012). Results of previously published studies varied regarding the efficacy of enteral nutrition versus drug therapy. Moreover, the external validity of these reports is limited by poor study design, small sample size, lack of GIB risk factor stratification, inconsistent GIB definitions, and/or variable enteral nutrition regimens.

A recent meta-analysis evaluated enteral nutrition on efficacy and safety outcomes for SUP. Analyses of pooled data of 14 trials showed that H_2RAs significantly reduced the risk of GIB versus controls in patients not receiving enteral nutrition (OR 1.47; 0.29–0.76; $p<0.002$). In a pooled analysis of three studies in which subjects were administered enteral feeds, the significant decrease in GIB previously observed with H_2RAs over controls was lost (OR 1.26; 0.43–3.7). This study also found that mortality and pneumonia rates were significantly higher in patients receiving H_2RAs and enteral nutrition than in patients receiving H2RAs without enteral feeds (Marik 2010). This study supports that SUP is not warranted once enteral feeds are initiated in ICU patients because of an increased risk of complications, and monotherapy with enteral feeds may provide sufficient benefit as a SUP agent.

Table 1-2. Summary of Comparative Meta-analyses for Stress Ulcer Prophylaxis: GI Bleeding and Pneumonia Rates

Study (Year)	Clinically Significant Bleeding Rates[a]	Pneumonia Rates
Cook (1991)	H_2RA vs. antacids (n=9) No significant difference OR = 0.84 (0.45–1.56) Antacids vs. sucralfate (n=5) No significant difference OR = 0.65 (0.16–2.49) H_2RA vs. sucralfate (n=1) No significant difference OR = 0.95 (0.06–15.4)	N/A
Tryba (1991)	H_2RA vs. sucralfate (n=9) Pooled data favor sucralfate over H_2RA OR = 0.532 (0.303–0.933) Antacids vs. sucralfate (n=10) No significant difference OR = 0.868 (0.452–1.667)	H_2RA vs. sucralfate (n=5) Pooled data show less risk with sucralfate than with H2RA; OR = 0.498 (0.316–0.783) Antacids vs. sucralfate (n=4) Pooled data show less risk with sucralfate than with antacids OR = 0.402 (0.235–0.687)

Table 1-2. (*Continued*)

Cook (1994)	H_2RA vs. antacids (n=9) No significant difference OR = 0.84 (0.45–1.56) Antacids vs. sucralfate (n=5) No significant difference OR = 1.39 (0.67–3.21) H_2RA vs. sucralfate (n=3) No significant difference OR = 1.05 (0.12–16.36)	Sucralfate vs. H_2RA/antacids (n=6) Decreased risk associated with sucralfate compared with H_2RAs or antacids OR = 0.50 (0.21–0.79)
Cook (1996)	H_2RA vs. antacids (n=10) No significant difference OR = 0.86 (0.46–1.59) Antacids vs. sucralfate (n=5) No significant difference OR = 1.49 (0.42–5.27) H_2RA vs. sucralfate (n=4) No significant difference OR = 1.28 (0.27–6.11)	H_2RA vs. antacids (n=3) No significant difference OR = 1.01 (0.65–1.57) Antacids vs. sucralfate (n=6) No significant difference OR = 0.80 (0.56–1.15) H_2RA vs. sucralfate (n=11) No significant difference OR = 0.83 (0.62–1.09)
Pongprasobchai (2009)	PPI vs. H_2RA (n=3) PPI superior efficacy over H2RA OR = 0.42 (0.20–0.91)	PPI vs. H_2RA (n=3) No significant difference OR = 1.02 (0.59–1.75)
Huang (2010)[b]	H_2RA vs. sucralfate (n=6) No significant difference Overt bleeding OR = 0.87 (0.49–1.53)	H_2RA vs. sucralfate (n=8) Decreased risk with sucralfate over H2RA OR = 1.32 (1.07–1.64)
Lin (2010)[c]	PPI vs. H_2RA (n=7) Pooled risk difference = -0.04 (-0.09 to 0.01) favoring PPIs over H2RAs	PPI vs. H_2RA (n=6) No significant difference Pooled risk difference = 0.00 (-0.04 to 0.05)
Barkun (2012)	PPI vs. H_2RA (n=6) PPI superior efficacy to H2RA OR = 0.39 (0.19–0.77)	PPI vs. H_2RA (n=6) No significant difference OR = 1.05 (0.69–1.62)
Alhazzani (2013)	PPI vs. H_2RA (n=12) PPI superior efficacy to H2RA RR = 0.36 (0.19–0.68)	PPI vs. H_2RA (n=8) No significant difference OR = 1.06 (0.73–1.52)

[a]Clinically significant bleeding rates reported unless otherwise stated.

[b]Clinically significant bleeding rates were not analyzed because only two trials met inclusion criteria definition, but a pooled analysis of six trials with overt bleeding rates was reported.

[c]Authors did not disclose all trials included in analysis; used definition of clinically significant bleeding.

H_2RA = histamine-2 receptor agonist; N/A = not applicable; OR = odds ratio; PPI = proton-pump inhibitor; RR = relative risk.

Information from Alhazzani W, Alenezi F, Jaeschke RZ, et al. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. Crit Care Med 2013a;41:693-705. Barkun AN, Bardou M, Pham CQ, et al. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. Am J Gastroenterol 2012;107:507-20. Cook DJ, Witt LG, Cook RJ, et al. Stress ulcer prophylaxis in the critically ill: a meta-analysis. Am J Med 1991;91:519-27. Cook DJ, Reeve BK, Scholes LC. Histamine-2-receptor antagonists and antacids in the critically ill population: stress ulceration versus nosocomial pneumonia. Infect Control Hosp Epidemiol 1994;15:437-42. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. JAMA 1996;275:308-14. Liu B, Liu S, Siddiqi J. Risks and benefits of stress ulcer prophylaxis in adult neurocritical care patients: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2015;19:409. Pongprasobchai S, Kridkratoke S, Nopmaneejumruslers C. Proton pump inhibitors for the prevention of stress-related mucosal disease in critically ill patients: a meta-analysis. J Med Assoc Thai 2009;92:632-7. Tryba M. Sucralfate versus antacids or H2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate. Crit Care Med 1991;19:942-9. Huang J, Cao Y, Liao C, et al. Effect of histamine-2-receptor antagonists versus sucralfate on stress ulcer prophylaxis in mechanically ventilated patients: a meta-analysis of 10 randomized controlled trials. Crit Care 2010;14:R194.

Despite these findings, the use of enteral nutrition alone as adequate SUP cannot be recommended because of the lack of corroboration from prospective, controlled clinical trials evaluating the safety and efficacy of enteral feeds on GIB.

Infectious Complications: Pneumonia and *Clostridium difficile*

Acid-suppressive therapy has increasingly been associated with an enhanced risk of infectious complications, predominantly nosocomial pneumonia and *C. difficile* infection (CDI). Although the mechanism leading to enteric infections and SUP remains unknown, some theories have been proposed. Gastric acidity has a pivotal role in preventing bacterial colonization. Reduced gastric acidity using acid-suppressive therapy may promote bacterial growth, bacterial translocation, or normal GI flora changes. In addition, PPIs have been proposed to have an immunosuppressive effect by impairing neutrophil function.

A pharmacoepidemiologic cohort study evaluated the incidence of pneumonia and CDI in 35,312 adult patients requiring mechanical ventilation for 24 hours or longer. Documented pneumonia was more common with PPIs than with H_2RAs (38.6% vs. 27.0%, respectively; p<0.001). *C. difficile* infections were also significantly more common with PPIs than with H_2RAs (3.8% vs. 2.2%, respectively, p<0.001). The risk of developing CDI was significantly higher in ICU patients receiving PPIs than in patients receiving H_2RAs (adjusted OR 1.29; 95% CI, 1.04–1.64) (MacLaren 2014b).

Another large retrospective study specific to medical ICU patients showed that PPIs increased the risk of developing CDI by 3-fold (OR 3.11; 95% CI, 1.11–8.74) (Buendgens 2014). Although several studies have shown that PPIs increase the risk of CDI more than H_2RAs, other reports have failed to corroborate these findings (Barletta 2014a; Tleyjeh 2013; Tleyjeh 2012; Shaughnessy 2011; Beaulieu 2007).

Similar to acid-suppressive therapy use and its association with developing CDI, the increased risk of pneumonia with these agents remains controversial. Use of PPIs was associated with an increased risk of pneumonia over H_2RAs (adjusted OR 1.2; 95% CI, 1.03–1.41). However, several meta-analyses that compared the risk of acquiring pneumonia between H_2RAs and PPIs in critically ill patients failed to show an association (Alhazzani 2013a; Barkun 2012; Lin 2010; Pongprasobchai 2009). The association between acid-suppressive agents and the true risk of pneumonia, as well as CDI, remains debatable because a causal relationship has not been established. Nonetheless, several reports suggest that PPIs lead to these infectious complications. Prudent use of these agents is warranted to avoid any unnecessary risks.

Cost-effectiveness Analysis

Several studies have examined the cost-effectiveness of acid-suppressive therapy in preventing stress-related GIB (Barletta 2014b; MacLaren 2014a; Barkun 2013; Udeh 2010). One report developed a decision analysis of bleeding comparing no prophylaxis with various intravenous and enteral acid-suppressive therapies. Oral PPIs were more cost-effective than intravenous PPIs, oral or intravenous H_2RAs, and sucralfate. Base-case analysis reported immediate-release omeprazole as the most cost-effective agent ($12,390 per case of clinically significant GIB avoided). The least favorable option was sucralfate ($37,880 per case avoided) (Udeh 2010).

Another cost-effective analysis compared H_2RAs with PPIs. Similar to the earlier study, this analysis estimated the incremental increase in cost as $1250 higher per person with H_2RAs than with PPIs (Barkun 2013). A third study performed a decision analysis model comparing H_2RAs and PPIs over a 9-day course for SUP. This study uniquely incorporated the estimated costs associated with acid-suppressive therapy (H_2RA and PPI) for GIB as well as other negative outcomes, including CDI and pneumonia events. The H_2RAs were more cost-effective than the PPIs, resulting in $1095 savings per person for the base-case analysis ($6707 and $7802 per person, respectively) (MacLaren 2014a). These findings contradict previous reports favoring PPIs over H_2RAs. Although the investigators accounted for costs associated with developing CDI, the variables with the greatest impact on this decision tree model were attributed to expenses surrounding GIB and ventilator-associated pneumonia treatment.

VENOUS THROMBOEMBOLISM

Epidemiology

The exact incidence of VTE in critically ill patients has been challenging to define because of heterogeneous patient populations, limitations in study methodology, inconsistency in diagnostic strategies, and the wide range in reported occurrence of deep venous thrombosis (DVT) of 10%–80% (Geerts 2002). In the absence of prophylaxis, DVT is estimated to occur in 30% of medical-surgical patients, 20%–50% of neurosurgical patients, 50%–60% of trauma patients, and up to 80% of orthopedic surgical patients (Attia 2001). The incidence of pulmonary embolism may be more difficult to define because the symptoms are nonspecific (e.g., shortness of breath, hypoxemia, tachycardia, hypotension), and concerns about the risk of intravenous contrast may preclude the use of CT angiography to diagnose pulmonary embolism. An estimated 10% of hospital deaths are pulmonary embolism related, and many of these cases are only diagnosed on autopsy (Sweet 2013). Rates of DVT and pulmonary embolism are significantly reduced with the use of thromboprophylaxis. A recent randomized controlled trial (RCT) of medical-surgical ICU patients receiving pharmacologic prophylaxis (PROTECT trial) found proximal DVT rates of 5%–6% and pulmonary embolism rates of 1%–3% (Cook 2011).

Because most literature in the critically ill population has focused on lower-extremity DVTs and pulmonary embolisms, less is known about the rates and significance of

upper-extremity DVTs (UEDVTs). Many UEDVTs are related to central venous catheters (e.g., internal jugular or subclavian veins) or peripherally inserted central catheters (e.g., basilic or brachial veins). A follow-up study from the PROTECT trial reported rates of non-leg thromboses of 2.2%, most of which were in a deep vein. Although UEDVTs are believed to carry a lower risk of pulmonary embolism than lower-extremity DVTs, this study found an 11-fold increased risk of pulmonary embolism in individuals with an UEDVT diagnosis compared with individuals without a DVT diagnosis. In addition, the risk of pulmonary embolism for patients with non-leg DVT was higher than for those with leg DVT (1 in 7 for non-leg DVT vs. 1 in 12 for leg DVT). This finding seems surprising but may be related to less aggressive anticoagulation practices with UEDVT or less diagnostic testing for pulmonary embolism in patients with lower-extremity DVTs who already have a clear indication for therapeutic anticoagulation (Lamontagne 2014). The effects of pharmacologic prophylaxis compared with no prophylaxis on UEDVT rates in critically ill patients are unknown.

Risk Factors

Many risk factors have been associated with the development of VTE (Box 1-3). Almost all critically ill patients have at least one risk factor for VTE, and many have several risk factors. However, there are no validated risk assessment tools in critically ill patients that can be used to accurately stratify patients according to VTE risk (Kahn 2012).

NONPHARMACOLOGIC VTE PROPHYLAXIS

Antithrombotic agents including unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) have become routine for pharmacologic prophylaxis in many hospitalized and critically ill patients. However, because of the increased incidence of bleeding in the ICU population, the benefit of anticoagulants may be outweighed by their risk. Patients with active bleeding typically have a contraindication to pharmacologic prophylaxis, but the risk of major bleeding in other patients may be hard to estimate. Unfortunately, many patients who are at a high risk of bleeding are also at a high risk of VTE (e.g., spinal cord injury).

Many risk factors for bleeding (e.g., thrombocytopenia, coagulopathy, renal impairment, head injury, spleen or liver lacerations) are not absolute contraindications to pharmacologic prophylaxis in isolation but should be considered when initiating pharmacologic prophylaxis. Guidelines on VTE prophylaxis in trauma from *Inflammation and the Host Response to Injury* list several potential contraindications to pharmacologic prophylaxis, given the lack of data showing safety. These include severe closed-head injury, intracranial hemorrhage, craniotomy, epidural catheter use or epidural hematoma, ongoing hemorrhage, coagulopathy, significant intra-abdominal solid organ injury managed nonoperatively, and spinal column fracture (Cuschieri 2008). Withholding VTE prophylaxis early after trauma is common, though most patients can receive pharmacologic prophylaxis within 3 days after admission. The VTE rate in trauma patients appears to

Box 1-3. Risk Factors for VTE

Factors present before ICU admission

- Surgery
- Trauma
- Sepsis
- Previous VTE
- Older age (> 65 yr)
- Inherited or acquired hypercoagulable states
- Obesity and metabolic syndrome
- Immobilization (e.g., bedrest, stroke)
- Malignancy and its treatment
- Cigarette smoking
- Oral contraceptives, pregnancy, hormone replacement therapy

Factors acquired in the ICU

- Central venous catheters
- Sepsis
- Prolonged immobility (e.g., sedation, paralysis)
- Acute medical illness (e.g., pneumonia, acute myocardial infarction, congestive heart failure)
- Mechanical ventilation

Factors in trauma patients

- Age > 40 yr
- Pelvic or lower-extremity fracture
- Spinal cord injury with paralysis
- Head injury (Abbreviated Injury Scale score at least 3)
- Prolonged mechanical ventilation (> 3 days)
- Venous injury
- Shock on admission (systolic blood pressure < 90 mm Hg)
- Major surgical procedure

Operative factors (ranked from higher to lower risk)

- Total hip arthroplasty
- Colectomy
- Abdominal aortic aneurysm
- Lower-extremity bypass
- Lobe/pneumonectomy
- Amputation
- Cholecystectomy (higher risk with open procedure)

Postoperative factors

- UTI
- Acute renal insufficiency
- Postoperative transfusion
- Perioperative myocardial infarction
- Pneumonia

VTE = venous thromboembolism.

Information from: Gangireddy C, Rectenwals JR, Upchurch GR, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg 2007;45:335-42; Geerts W, Cook D, Selby R, et al. Venous thromboembolism and its prevention in critical care. J Crit Care 2002;17:95-104; Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379:1835-46; and Knudson MM, Ikossi DG, Khaw L, et al. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg 2004;240:490-8.

increase after 4 days without pharmacologic prophylaxis, so evaluating for its initiation on a daily basis is important (Nathens 2007).

When the use of pharmacologic prophylaxis is considered unsafe, nonpharmacologic modalities including graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and inferior vena cava (IVC) filters are recommended.

Mechanical Prophylaxis

Overview and Mechanism of Action

Intermittent pneumatic compression devices involve intermittent compression of the extremities through inflatable sleeves attached to an air pump. The primary mechanism of action of IPC devices appears to be related to improvement in venous and arterial blood flow, as well as prevention of venous stasis. Some investigations have suggested that IPC devices improve fibrinolytic activity; this may be related to suppression of plasminogen activator inhibitor-1 and the resulting increases in tissue plasminogen activator (Comerota 1997). Other proposed mechanisms include increases in tissue factor pathway inhibitor resulting in suppressed factor VIIa concentrations, increases in prostacyclin resulting in reduced platelet aggregation, and enhanced nitric oxide synthesis resulting in vasodilation (Chen 2001). However, GCS exert a purely mechanical action: as elastic sleeves compress the extremities, the cross-sectional area of the veins decreases. This increases blood velocity, which reduces venous stasis.

Efficacy

Data supporting mechanical prophylaxis are of variable quality and are largely limited to surgical patient populations; recommendations for medically ill patients are based on extrapolated data. Compared with no prophylaxis, analyses of pooled data from the American College of Chest Physicians (ACCP) guidelines show that both IPC and GCS significantly reduce the incidence of symptomatic VTE in orthopedic and non-orthopedic surgical populations. A recent Cochrane review evaluated the results from 19 studies of GCS in largely orthopedic and general surgery populations and found similar results. The DVT rate was 9% in the GCS group and 21% in the control group (OR 0.33; $p<0.00001$), and the pulmonary embolism rate was 2% in the GCS group and 5% in the control group (OR 0.38; $p=0.04$) (Sachdeva 2014). Individual studies have failed to show a consistent reduction in pulmonary embolism when IPC or GCS are used alone.

Precautions and Adverse Effects

Mechanical prophylactic modalities are prone to poor adherence, and efficacy depends entirely on appropriate application. One center reported an adherence rate of 82% in surgical ICU patients and 62% in non-ICU surgical patients (Bockheim 2009). The ACCP guidelines recommend at least 18 hours of use daily; hence, adherence to these devices should be monitored to ensure the patient is receiving the prescribed therapy (Gould 2012).

Relative contraindications to mechanical prophylaxis include dermatitis, skin breakdown, or ulceration; peripheral vascular disease; lower-extremity bypass procedure; and lower-extremity trauma with plaster cast. Mechanical prophylactic methods are known to carry a risk of skin breakdown, ulcers, and necrosis, though this risk has not been well defined. These adverse events may occur in up to 5% of patients receiving these therapies for a prolonged period (Dennis 2009).

IVC Filters

Inferior vena cava filters are cage-like devices inserted into the IVC to prevent the embolization of a lower-extremity DVT to the lung. Inferior vena cava filters are often used for pulmonary embolism prevention in patients who cannot receive pharmacologic prophylaxis, but this practice remains controversial. The most established indication for an IVC filter is when a DVT is present but a contraindication to anticoagulation exists (Kearon 2012). The ACCP guidelines recommend against IVC filters for prophylactic use in surgical and trauma patients (Falck-Ytter 2012; Gould 2012).

When used for prophylaxis, retrievable filters are placed; these can be removed after the risk of thrombosis subsides. However, many retrievable filters may never be removed if patients are lost to follow-up or if documentation of the filter placement and plan is inadequate (Sarosiek 2013). Risks associated with IVC filters include device migration, embolization of device components, IVC perforation, and filter fracture (FDA 2010).

Prophylactic use of IVC filters may be most common in patients with major trauma who are at a high risk of both thrombosis and bleeding, and this population is the subject of most studies. A meta-analysis found a significant reduction in pulmonary embolism and fatal pulmonary embolism in trauma patients who received IVC filters. However, only one RCT was included in this analysis, and all studies were considered to have a moderate or high risk of bias (Haut 2014). In contrast, data from a registry of Michigan trauma centers showed no difference in adjusted mortality and an increased risk of DVT for patients who received IVC filters (Hemmila 2015). Because the presence of an IVC filter may influence the decisions surrounding anticoagulation, it is important to know whether a patient presents with a filter already in place. If not included in the patient's history, a filter is visible by imaging studies of the abdomen, including radiography and CT.

PHARMACOLOGIC AGENTS USED FOR VTE PROPHYLAXIS

Several pharmacologic agents have been studied for VTE prophylaxis in various patient populations. Each medication class carries its own advantages and disadvantages and, depending on the situation, may sometimes be preferred or

contraindicated. Understanding the pharmacokinetic and pharmacodynamic characteristics of these medications is essential to ensure safe and effective VTE prophylaxis.

Heparin Derivatives

Unfractionated Heparin

The benefits of heparin include its safety profile in renal dysfunction, relatively short duration of action, low cost, and availability of a reversal agent (protamine). Limitations of heparin for prophylaxis include its unpredictable subcutaneous absorption, interpatient variability in anticoagulant response, risk of heparin-induced thrombocytopenia (HIT), and long-term effects on bone metabolism, which can lead to osteoporosis. Monitoring is generally not indicated when heparin is used at prophylactic doses. However, the parameters used for monitoring the therapeutic dosing of heparin include the anti-factor Xa (anti-Xa) assay and the activated PTT (aPTT).

Controversy exists regarding the appropriate dose of UFH for VTE prophylaxis (i.e., 5000 units twice daily or three times daily). Both regimens have been studied in RCTs, but they have not been compared with each other directly. In addition, only the twice-daily regimen has been evaluated in RCTs of critically ill patients. A 2007 meta-analysis that incorporated all available RCTs at the time (12 studies) found no difference in the VTE rate for three times daily (3.5 per 1000 patient-days) versus twice daily (5.4 per 1000 patient-days, p=0.87); however, there was a trend toward lower rates of pulmonary embolism (0.5 vs. 1.5, p=0.09) and proximal DVT (0.9 vs. 2.3, p=0.05) and increased bleeding in the three-times-daily group (0.96 per 1000 patient-days vs. 0.35 per 1000 patient-days, p<0.001) (King 2007).

In contrast, a 2011 meta-analysis that included an additional four trials found no difference in any outcome. Comparing three-times-daily with twice-daily heparin, the relative risks of DVT, pulmonary embolism, death, and major bleeding were, respectively, 1.56 (95% CI 0.64–4.33), 1.67 (95% CI 0.49–208.09), 1.17 (95% CI 0.72–1.95), and 0.89 (95% CI 0.08–7.05) (Phung 2011). Some experts have suggested that three-times-daily heparin dosing should be used because of its reasonable safety profile and possible benefit over twice-daily heparin (Francis 2007), though the ACCP guidelines do not distinguish between the two (Kahn 2012). The decision to use one regimen over another may be based on the perceived risks of VTE and bleeding.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins have improved pharmacokinetic characteristics compared with UFH; moreover, their subcutaneous bioavailability is higher and more predictable, and their plasma half-life is prolonged. Low-molecular-weight heparins bind more selectively to factor Xa and may be monitored using the anti-Xa assay, though this is not routinely considered for prophylactic indications. Because dalteparin has a higher molecular weight than enoxaparin, it has reduced renal clearance and does not significantly accumulate in renal dysfunction when used at prophylactic doses (Atiq 2015).

Efficacy of UFH and LMWH in the Critically Ill Population

Unfractionated heparin and LMWH have been compared with each other and with placebo in several RCTs of critically ill patients (Table 1-3). The use of UFH or LMWH consistently reduces DVT more than placebo, Comparisons of UFH and LMWH have produced conflicting results, though most studies have found no difference in DVT rates in ICU populations.

The largest study, the PROTECT trial, was a multicenter RCT that compared UFH (5000 units twice daily) with dalteparin (5000 units daily) in 3764 adult medical-surgical critically ill patients. Exclusion criteria included major trauma, neurosurgery or orthopedic surgery, need for therapeutic anticoagulation, and weight less than 45 kg. Ultrasonography was performed twice weekly to diagnose DVTs; pulmonary embolisms were evaluated with CT angiography or ventilation-perfusion scan, if indicated. Mechanical prophylaxis was only allowed if the study drug had to be held because of bleeding risk or HIT. The primary outcome was the incidence of a new proximal DVT detected at least 3 days after randomization. Around 90% of patients were mechanically ventilated, and 83% had central venous catheters. Proximal DVTs were identified in 5.1% of patients receiving dalteparin and 5.8% of patients receiving UFH (HR [interquartile range {IQR}] 0.92 [0.68–1.23]; p=0.57). The outcomes of any pulmonary embolism and definite or probable pulmonary embolism were significantly lower in the dalteparin group (rate of any pulmonary embolism: 1.3% vs. 2.3%, p=0.01). Major bleeding occurred in 5.5% of patients receiving dalteparin and 5.6% of patients receiving UFH (p=0.98). In addition, HIT rates were not significantly different. The authors concluded that dalteparin was not superior to UFH in decreasing the incidence of proximal DVT in this population (Cook 2011). Given that the study was not designed to make conclusions on the outcome of pulmonary embolism, it is unclear whether that result was a real treatment effect related to dalteparin or a finding attributable to chance. A study large enough to adequately measure rare outcomes like pulmonary embolism and death would probably not be feasible. Furthermore, three-times-daily heparin and LMWH have not been compared.

Fondaparinux

Fondaparinux is a synthetic derivative of the pentasaccharide found in UFH that binds to antithrombin and potentiates its activity. This agent has FDA label approval for VTE prophylaxis in various surgical populations, including hip, knee, and abdominal surgical procedures. Of all heparin derivatives, fondaparinux is the most dependent on renal clearance for elimination (Table 1-4). Its half-life is considerably longer than that of other agents (17 hours vs. less than 8 hours for LMWHs) and is prolonged in patients with renal dysfunction.

Table 1-3. Summary of RCTs Evaluating UFH and LMWH in Critically Ill Patients

Author (Year) Design	Patient Population	Interventions	Screening Methods	VTE Rates	Major Bleeding Rate
UFH vs. placebo					
Cade (1982) Single center	119 medical-surgical ICU patients	UFH 5000 units BID vs. placebo	Daily 125I-labeled fibrinogen leg scanning	DVT: 13% in UFH vs. 29% in placebo; p<0.05	NR
Kapoor (1999) Multicenter	791 medical ICU patients	UFH 5000 units BID vs. placebo	US every 72 hr in ICU VQ scan for respiratory symptoms	DVT: 11% in UFH vs. 31% in placebo; p=0.001 Pulmonary embolism: 2.2% in UFH vs. 5% in placebo; p=NR	NR
LMWH vs. placebo					
Fraisse (2000) Multicenter	223 MV patients with COPD (169 assessable)	Nadroparin 65 IU/kg vs. placebo	Weekly US and venography	DVT: 15.5% in LMWH vs. 28.2% in placebo; p=0.045 Pulmonary embolism: 0% in both groups	5.6% in LMWH vs. 2.7% in placebo, p=0.28
LMWH vs. UFH					
Geerts (1996) Single center	344 patients with major trauma	Enoxaparin 30 mg BID vs. UFH 5000 units BID	Venography between days 10 and 14 and US if VTE suspected	Proximal DVT: 14.7% in heparin and 6.2% in enoxaparin; p=0.012 Pulmonary embolism: 0% in UFH vs. 0.8% in enoxaparin; p=NR	0.6% in UFH vs. 2.9% in enoxaparin; p=0.12
Goldhaber (2000) Multicenter	310 medical ICU patients	Enoxaparin 30 mg BID vs. UFH 5000 units BID	US on days 3, 7, 10, and 14	DVT: 16% in LMWH vs. 13% in UFH; p=NS	2% vs. 2% (p=NS)
Shorr (2009) Multicenter	1935 patients with sepsis receiving drotrecogin alfa	Enoxaparin 40 mg daily vs. UFH 5000 units BID vs. placebo	US between days 4 and 6	DVT: 5.6% in UFH vs. 5.9% in enoxaparin vs. 7% in placebo; p=NS Pulmonary embolism: 0.4% in UFH vs. 0.4% in enoxaparin vs. 0.8% in placebo; p=NS	NR
De (2010) Single center	156 surgical ICU patients	Enoxaparin 40 mg daily vs. UFH 5000 units BID	US between postoperative days 5 and 7	DVT: 2.7% in UFH vs. 1.2% in enoxaparin; p=0.51	2.7% in UFH vs. 1.2% in enoxaparin; p=0.48
Cook (2011) Multicenter	3764 medical-surgical ICU patients	Dalteparin 5000 units daily vs. UFH 5000 units BID	US within 2 days and twice weekly	Proximal DVT: 5.8% in UFH vs. 5.1% in dalteparin; p=0.57 Pulmonary embolism: 2.3% in UFH vs. 1.3% in dalteparin; p=0.01	5.6% in UFH vs. 5.5% in dalteparin; p=0.98

BID = twice daily; COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; MV = mechanically ventilated; NR = not reported; NS = not significant; PE = pulmonary embolism; RCT = randomized controlled trial; UFH = unfractionated heparin; US = ultrasonography; VQ = ventilation-perfusion.

Table 1-4. Dosing Recommendations for Heparin Derivatives

Agent	Usual Prophylactic Dose	Dose Adjustments
Heparin	5000 units SC BID or TID	N/A
Enoxaparin	40 mg SC daily 30 mg SC BID[a]	CrCl < 30 mL/min/1.73 m^2: 30 mg SC once daily or avoid. Consider anti-Xa monitoring for accumulation
Dalteparin	5000 units SC daily	CrCl < 30 mL/min/1.73 m^2: No adjustment. Consider anti-Xa monitoring for accumulation
Fondaparinux	2.5 mg SC daily	Weight < 50 kg: Avoid CrCl 30–50 mL/min/1.73 m^2: Reduce dose 50%[b] or avoid CrCl < 30 mL/min/1.73 m^2: Contraindicated, though doses of 2.5 mg SC q48hr[b] have been reported

[a]Dosing regimen commonly used in trauma patients

[b]Off-label recommendation.

q = every; SC = subcutaneously; TID = three times daily.

Information from: Manufacturers' package inserts; Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e24S-e43s; and Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 1996;335:701-7.

Anti-Xa activity for fondaparinux is not routinely monitored because assays calibrated for this agent are not widely available. Heparin-induced thrombocytopenia related to fondaparinux appears to be extremely rare, and there is increasing interest in using this agent in patients with suspected or confirmed HIT or a history of HIT (Garcia 2012).

Benefits of fondaparinux include convenience, predictable pharmacokinetics, and low risk of HIT. Limitations include drug acquisition costs, long half-life, accumulation in renal dysfunction, and lack of a reversal agent. Furthermore, no prospective randomized studies of fondaparinux have been conducted in critically ill patients. Because of the listed limitations for this product, its use in critically ill patients may be limited to select populations and clinical scenarios.

Other Agents

Direct Oral Anticoagulants

Direct oral anticoagulants include the thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. As a group, these agents offer the benefits of reliable pharmacokinetics, ease of administration, and generally favorable safety profiles. Limitations include lack of clinical experience and data compared with parenteral agents, lack of reliable monitoring tests to detect therapeutic concentrations or drug accumulation, concerns about erratic oral absorption in critically ill patients, impaired drug clearance in renal dysfunction or with drug interactions, and lack of specific reversal agents for the factor Xa inhibitors. Collectively, they carry indications for stroke prevention in nonvalvular atrial fibrillation, treatment of DVT/pulmonary embolism, and VTE prophylaxis. Only rivaroxaban and apixaban have FDA label approval for VTE prophylaxis; they are indicated for postoperative thromboprophylaxis after hip or knee replacement surgery. Clinical trials for extended prophylaxis in medically ill patients found an increased risk of bleeding compared with LMWH. No studies of direct oral anticoagulants have specifically evaluated critically ill patients; thus, their use in this population is limited at this time.

Warfarin

Vitamin K antagonists (VKAs), particularly warfarin, have been compared with both no prophylaxis and LMWHs in patients undergoing major orthopedic surgery. Compared with no prophylaxis, dose-adjusted VKAs (titrated to INR 2–3) significantly reduced the risk of pulmonary embolism and symptomatic DVT with nonsignificant trends toward increased major bleeding and reduced mortality. Data comparing LMWHs and VKAs generally favor LMWHs, finding a reduction in asymptomatic DVT in the initial treatment phase and an increased risk of bleeding with VKAs with extended prophylaxis. Benefits of VKAs include ease of oral administration, reversibility, cost, and relative safety in renal dysfunction. Limitations with VKAs are many and include intra- and interpatient variability in dose requirements, food and drug interactions, and need for regular laboratory monitoring. Although the ACCP guidelines prefer LMWHs to VKAs, VKAs may be a better option in certain patients (e.g., those with significant renal dysfunction and/or who refuse injections).

Comparative Cost-Effectiveness

The cost-effectiveness of one agent over another is influenced by acquisition costs, relative effects on VTE prevention,

and risk of adverse effects including major bleeding and HIT. Few studies have evaluated the cost-effectiveness of various agents in critically ill patients. A recent study investigated the cost-effectiveness of heparin versus dalteparin with data from the PROTECT trial. The authors evaluated costs derived from drugs, laboratory tests, personnel, diagnostic tests, procedures and operations, bleeding and blood product transfusion services, and infrastructure. They found a median cost of care of $40,805 (IQR $24,393–$76,139) in the UFH group and $39,508 (IQR $24,676–$71,431) in the dalteparin group (p=0.41). Dalteparin was no more expensive than UFH but was associated with a significantly lower incidence of pulmonary embolism and nonsignificant reductions in DVT and confirmed HIT. Sensitivity analyses showed that LMWHs remained similar in cost to, or less costly than, UFH except if the acquisition cost of dalteparin exceeded $179 per dose. Therefore, the authors concluded that dalteparin is the preferred agent for VTE prophylaxis from a health care payer perspective (Fowler 2014). These findings may or may not be translatable to every patient population, patients receiving UFH three times daily, or other patients receiving LMWHs, including enoxaparin.

ADVERSE EFFECTS ASSOCIATED WITH PHARMACOLOGIC VTE PROPHYLAXIS

Bleeding

For various reasons, many critically ill patients are at an increased risk of bleeding, which is the main adverse effect of concern with pharmacologic prophylaxis. The incidence of bleeding related to VTE prophylaxis varies greatly, depending on the baseline risk of the population, individual patient characteristics, and the agent chosen. In prospective studies specific to critically ill patients, LMWH (nadroparin) and UFH had no higher risk of major bleeding than placebo, with rates of 3%–4% for heparin derivatives and 3%–5% for placebo (p=0.32) (Alhazzani 2013b). Similarly, comparisons of LMWH and UFH found no difference in bleeding. The latter finding is largely influenced by the PROTECT trial, which found major bleeding rates of 5.5% in patients receiving dalteparin and 5.6% in patients receiving twice-daily UFH (p=0.98) (Cook 2011). Bleeding rates in prospective trials are low, but these studies have generally excluded patients at highest risk of bleeding. Risk factors associated with major bleeding in hospitalized medical patients include an active gastroduodenal ulcer, bleeding in the past 3 months, platelet count less than 50,000 cells/mm^3, age 85 or older, hepatic failure with an INR over 1.5, and renal failure with a glomerular filtration rate less than 30 mL/minute/1.73 m^2 (Decousus 2011).

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is a rare but potentially severe adverse effect that can arise from therapy with heparin and its derivatives. Heparin-induced thrombocytopenia may be fatal in 5%–10% of patients, mainly because of thrombosis, and the suggestion or diagnosis of HIT has significant implications for how to approach anticoagulant therapy (Linkins 2012).

Risk Factors and Diagnosis

The primary risk factor for developing HIT is the administration of heparin or its derivatives. Heparin carries the highest risk of HIT, which is reported to be as high as 5% in some populations. The risk is much lower with LMWH (less than 1%) and is negligible with fondaparinux. Patients undergoing surgery, particularly patients undergoing cardiac and orthopedic surgery, appear to have the highest risk of HIT, and the risk is also higher in women than in men.

In the absence of recent heparin exposure (about the past 100 days), thrombocytopenia in HIT begins to develop after 5–10 days of initial heparin exposure and is characterized by a fall in platelet counts to less than 150,000/mm^3 or a 50% decrease from baseline. Despite the patient's thrombocytopenia, bleeding in HIT is rare because of the procoagulable state. In some cases, rapid-onset HIT can occur in patients who were recently exposed to heparin and already have antibodies against the heparin–platelet factor 4 (PF4) complex. On heparin reexposure, platelet counts fall rapidly and significantly within 1 day.

Diagnosis of HIT is based on clinical suggestion and laboratory testing. Pretest probability may be determined using a screening tool such as the 4Ts score, which evaluates the degree of thrombocytopenia, timing, evidence of thrombosis, and other causes of thrombocytopenia. For suspected HIT (i.e., an intermediate or high 4Ts score), all forms of heparin (including LMWHs, heparin flushes, and heparin-impregnated catheters) should be discontinued and a non-heparin anticoagulant initiated (Linkins 2012).

Laboratory tests used to diagnose HIT broadly fall into two categories. Antigen assays detect antibodies against heparin-PF4 complexes and include the GTI-PF4 (Genetic Testing Institute, Waukesha, WI) and ID-PaGIA (Bio-Rad Laboratories, Berkeley, CA). Functional assays such as the serotonin release assay and heparin-induced platelet activation assay detect platelet activation in the presence of heparin. Antigen assays typically carry high sensitivity (95%–100%) but lower specificity (80%–90%) because some antibodies (especially non–immunoglobulin G [IgG]) may be nonpathogenic (Linkins 2012). Antigen assays are widely available with rapid turnaround times. Functional assays are more labor-intensive and expensive, and they are performed in fewer laboratories. However, they are specific for the diagnosis of HIT, so they are often used as confirmatory tests in the setting of a positive antigen assay.

If an enzyme immunoassay such as the GTI-PF4 is used, the magnitude of the result can improve the specificity of the test. Although the FDA-approved limit for a positive test is an

optical density (OD) greater than 0.4, less than 5% of patients with an OD of 0.4–1.0 have a positive functional assay (Linkins 2012). Furthermore, a positive correlation exists such that a patient with a higher OD (e.g., greater than 2) is much more likely to have confirmed HIT. These correlations may be considered when deciding to order a functional assay and evaluating how non-heparin anticoagulants should be managed.

Non-heparin Anticoagulants

For the treatment of HIT with or without thrombosis, the ACCP guidelines recommend lepirudin, argatroban, bivalirudin, or danaparoid, depending on the clinical context; however, lepirudin and danaparoid are no longer marketed in the United States (Linkins 2012). Bivalirudin is approved for use in patients undergoing percutaneous coronary intervention, including those with HIT, and is commonly prescribed for that indication. It has been used off-label for the treatment of confirmed or suspected HIT, and its use off-label has been supported by several retrospective studies. Argatroban, however, carries an indication for the treatment of HIT and is often the non-heparin anticoagulant of choice in critically ill patients. Limitations of argatroban include cost, unpredictable anticoagulant response and dose requirement, and risk of bleeding without an available reversal agent. Alternatives to the recommended agents include desirudin and fondaparinux, which are administered subcutaneously. Direct oral anticoagulants including dabigatran, rivaroxaban, and apixaban are attractive options for select patients, but only case reports of their use in HIT exist at this time. Details of non-heparin anticoagulants are listed in Table 1-5.

Table 1-5. Non-heparin Anticoagulants

	Argatroban	Desirudin	Bivalirudin	Fondaparinux
FDA approved for HIT	Yes	No	Yes (PCI with HIT)	No
Mechanism of action	Direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Elimination half-life	40–50 min	120 min	25 min	17–20 hr
Elimination	Hepatobiliary	Renal	80% enzymatic 20% renal	Renal
Dosing	Initial: 2 mcg/kg/min	Isolated HIT: 15 mg SC BID[a] HIT with thrombosis: 30 mg SC BID[a]	PCI: 0.75 mg/kg bolus then 1.75 mg/kg/h during the procedure and up to 4 hr after HIT: Initial infusion of 0.15–0.2 mcg/kg/hr[a]	Isolated HIT or prophylaxis with history of HIT: 2.5 mg SC daily[a] HIT with thrombosis: 5–10 mg SC daily depending on body weight[a]
Dose adjustments	Critically ill with multiorgan dysfunction: Consider starting as low as 0.2 mcg/kg/min Moderate to severe hepatic impairment: Start at 0.5 mcg/kg/min or lower	Renal impairment: Dosing not defined for this indication; consider avoiding	Renal dysfunction: Doses as low as 0.03 mcg/kg/hr may be required in severe renal dysfunction	CrCl 30–50 mL/min/1.73 m^2: Use caution, consider 50% dose reduction[a] CrCl < 30 mL/min/1.73 m^2: Contraindicated, though doses of 2.5 mg SC q48hr have been reported
Monitoring	aPTT	aPTT	aPTT	Anti-Xa assay
Effect on INR	Excessive	Minimal	Moderate	None

[a]Off-label dose.

HIT = heparin-induced thrombocytopenia; PCI = percutaneous coronary intervention.

Information from: Manufacturers' package inserts; and Boyce SW, Bandyk DF, Bartholomew JR, et al. A randomized, open-label pilot study comparing desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis: PREVENT-heparin-induced thrombocytopenia study. Am J Ther 2011;18:14-22.

Data for desirudin and fondaparinux are limited, though these agents generally appear to be safe and effective in the treatment of HIT. Desirudin was compared with argatroban in one open-label randomized study of 16 patients, which was terminated early because of poor enrollment (Boyce 2011). No patients randomized to desirudin had new or worsening VTE. Fondaparinux has not been evaluated in any randomized trials; several case reports, case series, and retrospective studies have explored its use in HIT. A recent retrospective study used propensity matching to compare 239 patients who received non-heparin anticoagulants for suspected HIT. Patients who received fondaparinux (n=133) were compared with those who received danaparoid (n=59) or argatroban (n=47). Around 60% of patients in the fondaparinux group received prophylactic dosing (2.5 mg subcutaneously daily). Overall, there was no difference in rates of thrombosis or major bleeding between groups. When evaluating only patients with confirmed HIT, thrombosis rates were similar between fondaparinux and danaparoid/argatroban (16% vs. 25%, respectively, p=0.246), though bleeding rates trended higher (36% vs. 5%, p=0.008) in the matched cohort (Kang 2015). This study provides support for using fondaparinux in the empiric treatment of HIT, including prophylactic dosing when VTE is not present, though prospective studies are required to definitively show the safety and efficacy of this approach. Case reports of HIT from fondaparinux exist, though cross-reactivity between heparin-dependent IgG antibodies and fondaparinux is not reported (Warkentin 2011).

VTE PROPHYLAXIS RECOMMENDATIONS IN SELECT PATIENT POPULATIONS

ACCP Guideline Recommendations

Preferred VTE prophylaxis for specific populations as recommended in the ACCP guidelines is listed in Table 1-6.

Obesity

Obesity is a known risk factor for developing VTE, and many of the drugs used for VTE prophylaxis are influenced by excess adipose tissue. Usual recommendations for VTE prophylaxis, which have generally not considered this, suggest a similar dose regardless of body weight. Limited evidence to guide dosing in this population is available, especially in critically ill and nonsurgical populations. Studies evaluating anti-Xa concentrations in patients with obesity receiving LMWH have often found an inverse relationship between body weight and anti-Xa level; however, the association between anti-Xa concentrations and risk of VTE, and the ideal anti-Xa peak or trough for VTE prophylaxis, is uncertain. Many studies have evaluated various dosages, primarily with enoxaparin. Trial data with the most validated clinical outcomes is for a regimen of enoxaparin 40 mg twice daily (Vandiver 2016). Increased doses of UFH are often recommended, but this strategy is not well supported by prospective studies.

A retrospective review analyzed 9241 inpatients weighing over 100 kg who received VTE prophylaxis with enoxaparin or UFH. Standard-dose prophylaxis (enoxaparin 40 mg daily or UFH 5000 units twice or three times daily) was compared with high-dose prophylaxis (enoxaparin 40 mg twice daily or UFH 7500 units three times daily). There were no differences in VTE rates, regardless of prophylactic strategy, in patients with a BMI less than 40 kg/m^2. However, at BMIs of 40 kg/m^2 or more, VTE rates were lower in the high-dose prophylaxis group (0.8% vs. 1.5%, p=0.05). Bleeding events occurred in 7%–8% of patients and did not differ between groups (Wang 2014).

Given the results of this retrospective trial and other prospective trials of the bariatric surgery population, it seems reasonable to prescribe enoxaparin 40 mg twice daily or heparin 7500 units three times daily in patients with a BMI 40 kg/m^2 or more, assuming a normal bleeding risk and no other contraindications (e.g., HIT, or renal impairment for enoxaparin). More prospective studies are needed to confirm these findings and better characterize the ideal VTE prophylactic regimen for various body weights.

Practice Points

Many challenges face clinical pharmacists in their efforts to optimize acid-suppressive therapy and anticoagulants in the ICU. Conflicting data and/or the paucity of studies in certain special populations poses a challenge for clinicians to adopt a consensus on cost-effective therapy. Although institutions should strive to reach a consensus on preferred therapies for supportive and preventive care, individualized approaches should also be incorporated.

- **The association of infectious complications with acid-suppressive therapies remains debated. However, this should be factored into clinical decision-making.**
- **Published clinical guidelines on SUP management are conflicting, leaving many clinicians uncertain regarding optimal management.**
- **Various cost-effective studies also report differences in the optimal agent selection; however, the most recently published report and robust study incorporating infectious complications suggests H_2RAs are the preferred agent.**
- **LMWH and UFH are viable options for VTE prophylaxis in ICU patients, according to individual studies and clinical practice guidelines.**
- **Risk factor stratification and risk of bleeding should be assessed in each patient to determine the optimal agent, especially in special populations.**
- **Pharmacists should be involved in agent selection, duration, risk factor stratification, and evaluation of risk of deleterious events for both SUP and VTE prophylaxis.**

Table 1-6. Recommendations for VTE Prophylaxis in Various Populations

Risk of VTE	Risk of Bleeding	Prophylaxis
Critically Ill Medical Patients		
Any	Low	LMWH or UFH
Any	High	Mechanical (GCS or IPC)[a]
General and Abdominal-Pelvis Surgical Patients		
Very low	N/A	Early ambulation
Low	N/A	IPC
Moderate	Low	LMWH, UFH, or IPC
	High	IPC
High	Low	LMWH or UFH plus IPC
	Low (contraindications to UFH, LMWH)	Low-dose aspirin, fondaparinux, IPC
	High	IPC[a]
Orthopedic Surgery Patients		
Total hip arthroplasty or total knee arthroplasty	Low	LMWH (preferred)[b], fondaparinux, apixaban, dabigatran, rivaroxaban, UFH, VKA, aspirin, or IPC Duration: At least 10–14 days
Hip fracture surgery	Low	LMWH (preferred),[b] fondaparinux, UFH, VKA, aspirin, or IPC Duration: At least 10–14 days
Any major orthopedic surgery	High	IPC[a]
Major Trauma Patients		
Low-moderate	Low	LMWH, UFH, or IPC[d]
High[c]	Low	LMWH or UFH plus mechanical prophylaxis[d]
Any	High	IPC[a,d]

[a]Start pharmacologic prophylaxis when bleeding risk subsides.

[b]Begin at least 12 hr or more preoperatively or at least 12 hr postoperatively.

[c]Includes acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma.

[d]If not contraindicated by lower-extremity injury.

GCS = graduated compression stockings; IPC = intermittent pneumatic compression; VKA = vitamin K antagonist.

Information from: Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e278S-325S; Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e227S-77S; and Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e195S-226S.

CONCLUSION

The pharmacist plays a definite role in supportive and preventive care in the ICU. Use of acid suppression and anticoagulants is effective but is associated with potential adverse events. Controversy has surrounded the optimal use of both acid-suppressive therapy and anticoagulants in ICU patients. Although there is no consensus among institutions, health care providers should evaluate individual practices to use evidence-based therapy. Variability in risk factors in ICU patients for stress ulcer bleeding and VTE poses a challenge to adopt a comprehensive strategy to individualize care in the manner of a protocol and/or clinical pathway. The pharmacist plays a pivotal role in

prudent medication use in the critically ill population, including special patient populations in the ICU. Pharmacists must promote the most cost-effective therapy in the ICU while delivering individual care to meet the need of each patient.

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Self-Assessment Questions

1. A 59-year-old man is admitted to the ICU for severe community-acquired pneumonia and a possible chronic obstructive pulmonary disease (COPD) exacerbation resulting in acute respiratory failure. Subsequently, he requires endotracheal intubation with mechanical ventilation. The following drugs are initiated: levofloxacin 750 mg orally daily, albuterol 2.5 mg nebulized every 4 hours, ipratropium 0.5 mg nebulized every 4 hours, and prednisone 40 mg orally daily. Which one of the following best describes the total number of risk factors for stress-related mucosal disease in this patient?

   A. One
   B. Two
   C. Three
   D. Four

2. A 68-year-old woman was admitted to the ICU for septic shock. She is now hemodynamically stable without requiring further vasoactive support. In addition, she was extubated 72 hours ago and can now sit up in a chair. Her drugs are cefepime 2 g intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, and hydrocortisone 50 mg intravenously every 6 hours. The patient has no medical history requiring acid-suppressive therapy, but she is currently receiving your institution's preferred stress ulcer prophylaxis (SUP) agent of choice. Which one of the following is best to recommend as a time to discontinue this patient's SUP strategy?

   A. After hydrocortisone is discontinued or tapered to less than 200 mg
   B. Immediately
   C. Upon ICU discharge
   D. Upon hospital discharge

3. A 67-year-old man is admitted to the ICU for a severe COPD exacerbation requiring endotracheal intubation with mechanical ventilation. Other comorbidities include congestive heart failure, diabetes mellitus, and end-stage renal disease requiring hemodialysis. His APACHE II score on admission is 28. The patient is currently receiving vasoactive support with norepinephrine, and continuous renal replacement therapy is expected to begin in the next 24 hours. Which one of the following risk factors best justifies SUP for this patient?

   A. APACHE II score
   B. Mechanical ventilation
   C. End-stage renal disease
   D. COPD exacerbation

4. A 45-year-old man is admitted to the cardiac ICU after undergoing percutaneous coronary intervention with a bare metal stent. Dual antiplatelet therapy consisting of aspirin and clopidogrel is initiated. The cardiac surgeon wants to initiate the patient on the proton pump inhibitor (PPI) of your choice. Which one of the following is best to recommend for this patient?

   A. Lansoprazole 30 mg orally daily
   B. Lansoprazole 30 mg disintegrating tablet by feeding tube daily
   C. Pantoprazole 40 mg orally daily
   D. Omeprazole 40 mg bicarbonate solution by feeding tube daily

5. During patient care rounds, the intensivist discusses the patients most appropriate to receive SUP. He argues that all patients in the ICU should receive acid-suppressive therapy because most patients have some degree of GI mucosal damage shortly after admission. Which one of the following education points is best to share with this colleague?

   A. Acid-suppressive therapy is directly linked to infectious complications.
   B. The severity of illness among all ICU patients may vary.
   C. The incidence of GI mucosal damage resulting in clinical important bleeding is low.
   D. Tachyphylaxis may develop in patients who are receiving prolonged therapy.

6. A 47-year-old woman was recently admitted to the ICU for presumed sepsis and pneumonia. She has a medical history of end-stage liver disease and dialysis-dependent chronic kidney disease. The attending ICU physician initiated famotidine as his SUP agent of choice upon admission. Seven days after admission, the patient still requires mechanical ventilation, norepinephrine, and continuous renal replacement therapy. Other pertinent therapies include cefepime and vancomycin for empiric antimicrobial coverage (despite negative cultures) and heparin 5000 units subcutaneously every 8 hours. Her platelet count on ICU day 7 is 62,000/mm^3. Which one of the following is best to recommend regarding SUP for this patient?

   A. Change famotidine to cimetidine.
   B. Change famotidine to pantoprazole.
   C. Continue famotidine without any further intervention.
   D. Continue famotidine and add pantoprazole.

7. A 69-year-old man is admitted to the trauma ICU with abdominal penetrating trauma and right leg open femur fracture after a motor vehicle crash. The patient is receiving mechanical ventilation. On hospital day 3, he still cannot tolerate enteral feeds, so parenteral nutrition is initiated. The trauma attending wants to initiate a PPI for SUP and discusses the potential complications with the multidisciplinary team of using this pharmacologic class. Which one of the following is best to recommend for this patient?

   A. Start famotidine because of the hypomagnesemia risk with PPIs and parenteral nutrition.
   B. Start famotidine because of the concern for PPI use in a patient with a femur fracture.
   C. Start famotidine because the vitamin B_{12} deficiency risk with PPIs is higher with parenteral nutrition.
   D. Initiate a PPI because the risk of bone fractures or hypomagnesemia is unlikely in this patient.

Questions 8 and 9 pertain to the following case.

G.T. is a 24-year-old man with a traumatic brain injury. On ICU admission, he has a Glasgow Coma Scale score of 5 and requires endotracheal intubation with mechanical ventilation. The medical institution enables ICU physicians to choose their preferred SUP agent; G.T.'s physician uses famotidine. On ICU day 8, G.T. develops ventilator-associated pneumonia. The physician is concerned about the association between acid-suppressive therapy and this new-onset pneumonia. The ICU physician informs you that she believes G.T. is at an extremely low risk of developing stress-related mucosal bleeding.

8. Which one of the following points about the association between pneumonia and acid-suppressive use is best to discuss with the ICU physician caring for G.T.?

   A. RCTs have consistently shown a higher risk of developing pneumonia with PPIs than with histamine-2 receptor antagonists (H_2RAs).
   B. Observational, cohort trials have consistently shown a higher risk of developing pneumonia with PPIs than with H_2RAs.
   C. RCTs have consistently shown no difference in the risk of developing pneumonia between PPIs and H_2RAs.
   D. Observational, cohort trials have consistently shown no difference in the risk of developing pneumonia between PPIs and H_2RAs.

9. Three days later, G.T.'s condition has not improved. He has developed diarrhea with a concern for *Clostridium difficile* infection. Which one of the following would be most cost-effective for G.T.?

   A. Give a PPI.
   B. Give an H_2RA.
   C. Give sucralfate.
   D. Discontinue all acid-suppressive therapy.

10. A multidisciplinary task force is formed at your institution with the goal of addressing best practices for SUP therapy throughout the hospital. Which one of the following statements best represents recommendations based on published data over "expert opinion" as a reasonable approach to implementing a policy for SUP?

    A. PPIs should be the recommended agent because the Surviving Sepsis Campaign and Danish Society of Intensive Care Medicine guidelines prefer this agent.
    B. H_2RAs should be the recommended agent because they may be the most cost-effective approach.
    C. H_2RAs or PPIs should be the recommended agent because the Surviving Sepsis Campaign and Danish Society of Intensive Care Medicine guidelines recommend either agent.
    D. H_2RAs or PPIs should be recommended because both have cost-effective analyses supporting their use.

11. A 35-year-old woman is admitted to the surgical ICU after a laparoscopic cholecystectomy for acute cholecystitis. She is febrile and tachycardic and has a lactate concentration of 5.2 mmol/L (normal range 0.5–1 mmol/L), consistent with severe sepsis. The patient was treated 2 years ago for a deep venous thrombosis (DVT) related to oral contraceptives, which she no longer takes. Which one of the following best describes this patient's current risk factors for venous thromboembolism (VTE)?

    A. Age, surgery, and oral contraceptives
    B. Surgery, history of DVT, and fever
    C. Age, surgery, and hyperlactatemia
    D. Sepsis, surgery, and history of DVT

12. A 62-year-old man is admitted to the neurosciences ICU after a large middle cerebral artery infarct. He has an inferior vena cava (IVC) filter that was placed 5 years ago after receiving a diagnosis of a left femoral vein DVT. On day 6, he is given a workup for fever and undergoes ultrasonography, which reveals an upper-extremity DVT (UEDVT) at the site of his previous central venous catheter. Lower-extremity ultrasonography is negative for DVT. Which one of the following best describes this patient's risk of pulmonary embolism?

    A. He is protected from pulmonary embolism because of his IVC filter.
    B. His risk of pulmonary embolism is elevated, and he is not protected by his IVC filter.
    C. He is not at risk of pulmonary embolism because UEDVTs do not lead to pulmonary embolism.
    D. His risk of pulmonary embolism is very high because of the location of his new DVT.

13. A 53-year-old man (height 67 inches, weight 138 kg) underwent Roux-en-Y gastric bypass surgery 6 days ago. Today he develops fever, tachycardia, hypotension, and nausea. He is brought to the operating room for exploration. A leak at the gastrojejunal anastomosis is discovered and repaired, and a drain is placed. He returns to the ICU with improved hemodynamics. The patient has normal renal and hepatic function, and heparin 5000 units subcutaneously twice daily is ordered for VTE prophylaxis. Which one of the following is best to recommend as pharmacologic prophylaxis for this patient?

    A. Continue heparin 5000 units subcutaneously twice daily.
    B. Switch to a low-dose heparin infusion targeted to an anti-Xa concentration of 0.1–0.3 unit/mL.
    C. Switch to fondaparinux 10 mg subcutaneously daily.
    D. Switch to enoxaparin 40 mg subcutaneously twice daily.

Questions 14 and 15 pertain to the following case.

G.R. is a 44-year-old man admitted to the medical ICU with septic shock and acute respiratory failure from community-acquired pneumonia. After intubation, a significant amount of coffee ground–appearing material is suctioned from his nasogastric tube. Laboratory values after transfer from the ED show a drop in Hgb from 10.9 g/dL to 7.4 g/dL (2 hours apart) and a coagulopathy with an INR of 2.2.

14. Which one of the following is best to recommend as VTE prophylaxis for G.R.?

    A. He is "auto-anticoagulated" and thus does not require additional prophylaxis.
    B. Give mechanical prophylaxis with intermittent pneumatic compression (IPC).
    C. Give enoxaparin 40 mg subcutaneously daily.
    D. Give heparin 5000 units subcutaneously twice daily.

15. Given the concern for an upper GI bleed, G.R. undergoes endoscopic evaluation, which reveals a normal esophagus, stomach, and duodenum. Over the next 2 days, his hemoglobin remains stable, platelet count is within normal range, and INR is 1.4. Suctioned gastric contents appear bilious with no evidence of blood. His shock has improved, though he has developed acute kidney injury with an SCr that has increased from 0.8 mg/dL on admission to 2.2 mg/dL. Which one of the following is best to recommend as VTE prophylaxis for G.R.?

    A. Mechanical prophylaxis with IPC
    B. Enoxaparin 40 mg subcutaneously daily
    C. Heparin 5000 units subcutaneously three times daily
    D. Fondaparinux 2.5 mg subcutaneously daily

Questions 16 and 17 pertain to the following case.

H.P. is a 71-year-old woman who was admitted to your hospital last month after a fall. She was discharged home 10 days ago and today presents with tachycardia, shortness of breath, and hypoxemia. Given her recent immobility and infection, there is concern for a pulmonary embolism; a CT angiography scan reveals multiple bilateral segmental and subsegmental filling defects consistent with thrombi. H.P. is given an intravenous bolus of heparin and initiated on a heparin drip. The next day, her platelet count has decreased from 277,000/mm^3 to 98,000/mm^3, her respiratory status has declined further, and her SCr has increased from 0.8 mg/dL to 1.8 mg/dL. An echocardiogram reveals new right ventricular strain that was not present on admission. The team suspects heparin-induced thrombocytopenia (HIT) (you confirm heparin exposure during her recent previous admission) and worsening pulmonary embolism, despite a therapeutic aPTT on heparin. H.P.'s hepatic function is normal.

16. Which one of the following is best to recommend regarding H.P.'s anticoagulation?

    A. Continue heparin and consider other therapies for pulmonary embolism, including thrombolysis.
    B. Discontinue heparin, send a heparin-PF4 antibody assay and serotonin release assay, and use mechanical prophylaxis until HIT studies return.
    C. Discontinue heparin, send a serotonin release assay, and initiate fondaparinux at 5 mg subcutaneously daily.
    D. Discontinue heparin, send a heparin-PF4 antibody assay, and initiate argatroban at 1 mcg/kg/minute.

17. H.P. continued to receive heparin; a heparin-PF4 antibody test 2 days later showed an optical density of 1.254 (normal range less than 0.4). Her platelet count is now 115,000/mm^3, and she has improved clinically from a respiratory and cardiovascular perspective. Which one of the following is best to recommend for H.P.'s anticoagulation?

    A. Send a serotonin release assay and change heparin to argatroban.
    B. Continue heparin with a therapeutic aPTT goal.
    C. Send a serotonin release assay and continue heparin with a therapeutic aPTT goal.
    D. Change heparin to argatroban and repeat the heparin-PF4 antibody test to assess for a previous false-positive result.

18. A 19-year-old man presents to the hospital after a motor vehicle crash. His injuries include several rib fractures, left-sided pneumothorax, and unstable fractures to several thoracic vertebrae, for which he undergoes internal fixation of the thoracic spine. Which one of the following is best to recommend as VTE prophylaxis for this patient?

A. Give heparin 5000 units subcutaneously three times daily.
B. Give enoxaparin 40 mg subcutaneously daily plus IPC.
C. Give fondaparinux 2.5 mg subcutaneously daily plus IPC.
D. Insert an IVC filter, and initiate a low-molecular-weight heparin after 3–5 days.

19. An 81-year-old woman recently underwent hip fracture surgery for a femoral neck fracture. She has a history of chronic kidney disease with a baseline SCr of 2.2 mg/dL. Which one of the following is the best agent for VTE prophylaxis to recommend for this patient?

A. Dalteparin 5000 units subcutaneously daily
B. Warfarin adjusted to an INR of 2–3
C. Fondaparinux 2.5 mg subcutaneously every other day
D. IPC

20. A 53-year-old man (weight 73 kg) is admitted to the medical ICU from a nursing home with acute respiratory distress syndrome from health care–associated pneumonia. He was hospitalized 6 months ago for a similar condition, and his course was complicated by confirmed HIT without thrombosis. He was treated with 3 months of warfarin. His platelet count is 320,000/mm^3 and SCr is 0.7 mg/dL. Which one of the following is best to recommend as VTE prophylaxis for this patient?

A. Argatroban infusion titrated to an aPTT 1.5–3 times baseline
B. Warfarin adjusted to an INR of 2–3
C. Heparin 5000 units subcutaneously three times daily
D. Fondaparinux 2.5 mg subcutaneously daily

Learner Chapter Evaluation: Prophylaxis of Stress Ulcer and Deep Venous Thrombosis.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Analyze major risk factors for clinically significant GI bleeding associated with stress-related mucosal disease.
13. Develop an evidence-based strategy for managing stress ulcer prophylaxis in the ICU setting.
14. Analyze major risk factors for venous thromboembolism (VTE) in the critically ill population.
15. Design an evidence-based strategy for VTE prophylaxis in the ICU.
16. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Perioperative Management: Cardiac and Vascular Surgery

By James C. Coons, Pharm.D., BCPS-AQ Cardiology; and
Matthew R. Wanek, Pharm.D., BCPS, BCCCP

Reviewed by William J. Peppard, Pharm.D., BCPS; and Julianna W. Gachoya, Pharm.D., BCPS, MBA-MHA

LEARNING OBJECTIVES

1. Design evidence-based therapeutic regimens to improve outcomes in post-cardiac surgery patients.
2. Apply strategies for supportive care in patients requiring mechanical circulatory support.
3. Design therapeutic regimens to treat and prevent complications in vascular surgery patients.
4. Evaluate for potential complications after cardiac surgery, and apply evidence-based strategies to prevent and/or treat them.

ABBREVIATIONS IN THIS CHAPTER

CABG	Coronary artery bypass grafting
CDT	Catheter-directed thrombolysis
CPB	Cardiopulmonary bypass
ECMO	Extracorporeal membrane oxygenation
HIT	Heparin-induced thrombocytopenia
LVAD	Left ventricular assist device
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
PAH	Pulmonary arterial hypertension
PCC	Prothrombin complex concentrate
PH	Pulmonary hypertension
POAF	Postoperative atrial fibrillation
RV	Right ventricle

Table of other common abbreviations.

INTRODUCTION

Both the global burden of cardiovascular disease (CVD) and the age of the population continue to rise. It is estimated that in the United States alone, more than 85 million people have at least one type of CVD, and about one-half are at least 60 years of age. By 2030, it is expected that 44% of the U.S. population will have some form of CVD (Mozaffarian 2015). Patient acuity, procedure complexity, and the associated challenges posed in designing rational pharmacotherapy mandate a high level of proficiency for the clinical pharmacist in the cardiovascular surgical setting. Pharmacists have many challenges in ensuring the safe and effective use of drugs for these patients while minimizing the impact on health care resources. These challenges include the introduction of novel agents, evolution of innovative surgical procedures and devices, and changes in evidence and guideline recommendations. This chapter focuses on the pharmacotherapeutic treatment of patients who undergo a variety of cardiac and vascular surgical procedures and the perioperative and postoperative complications that invariably ensue.

PERIOPERATIVE MANAGEMENT IN CARDIAC SURGERY

Coronary artery bypass grafting (CABG) is the most common cardiac surgical procedure performed, with almost 400,000 cases each year in the United States. The volume and risk-adjusted mortality of CABG procedures have declined over the past decade. The in-hospital mortality rate (deaths per 100 CABG discharges) in all age and sex subsets of patients has also declined, even with an increase in the Charlson comorbidity index (Mozaffarian 2015). Despite the

improved clinical outcomes related to cardiac open-heart surgery, patients who undergo CABG remain at high risk of ischemic events because of coronary artery disease (CAD) progression and vein graft atherosclerosis. Therefore, vigilant risk factor modification and pharmacologic therapies for perioperative management and secondary prevention are essential (Table 2-1).

The American College of Cardiology/American Heart Association has developed guideline recommendations for the optimal management of antiplatelets, β-blockers, lipids, ACE inhibitors, blood pressure, diabetes mellitus, smoking cessation, and infection management for these patients (Kulik 2015). Recommendations relating to aspirin and β-blocker use in the perioperative management of CABG are particularly compelling and (in some cases) controversial and are discussed in greater context later in the chapter.

Antiplatelet therapy with aspirin after cardiac surgery is a mainstay of cardiovascular prevention based on more than 30 years of experience. Platelet inhibition by aspirin results in improved vein graft patency rates as well as decreased CABG-related morbidity and mortality. Treatment protocols, dosing, and timing of initiation vary in the literature; however, the ideal time may be within 6 hours after CABG (Kulik 2015).

The Aspirin and Tranexamic Acid for Coronary Artery Surgery study prospectively randomized 2100 patients to preoperatively receive either 100 mg of aspirin or placebo, then evaluated a 30-day composite of death or thrombotic complications. Patients enrolled had not taken aspirin regularly before surgery or had discontinued aspirin at least 4 days before surgery. Overall, there were no differences between groups in the primary composite outcome (19.3% in the aspirin group vs. 20.4% in the placebo group; RR 0.94; 95% CI, 0.80–1.12; p=0.55) or in major hemorrhage leading to reoperation (1.8% in the aspirin group vs. 2.1% in the placebo group; p=0.75) (Myles 2016). Relevant to the safety end point, however, was that half of the patients received antifibrinolytic therapy as part of the 2 × 2 factorial design. In summary, all patients who undergo CABG should be considered candidates for long-term aspirin therapy. In fact, aspirin users over a 4-year period after surgery have significantly better long-term survival than do non-users (RR of death 0.58; 95% CI, 0.47–0.70) (Johnson 1992). However, the utility of preoperative aspirin is less certain, especially among patients who have not taken it regularly or among those who have discontinued it several days before surgery.

β-Blocker therapy continues to be an important intervention for secondary prevention in patients who undergo CABG. The most compelling data exist in the settings of post-myocardial infarction (MI), left ventricular dysfunction, and chronic heart failure. Early observational studies also suggested an improvement in 30-day mortality when β-blockers were used in the context of preoperative CABG (adjusted OR 0.94; 95% CI, 0.91–0.97) (Ferguson 2002). In the early to mid-2000s, several quality improvement projects fueled the adoption of β-blockers after CABG as part of efforts to enhance secondary prevention benchmarks after CABG (Kulik 2015). Some post-CABG data support an association between a lower risk of death or MI, whereas other data among stable patients with a history of CAD or MI (or risk factors only) show no difference in outcomes with β-blockers (Bangalore 2012; Goyal 2007). Nonetheless, many patients continue to receive β-blocker therapy preoperatively (Kulik 2015).

Continuing preoperative β-blockade into the postoperative setting, however, remains controversial. Mortality data in

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to postoperative atrial fibrillation in cardiac surgery
- Drug knowledge of the antiarrhythmic agents used to treat atrial fibrillation
- Drug knowledge of the common intravenous vasoactive agents used to treat shock
- General knowledge of the pathophysiology of pulmonary hypertension
- General pharmacologic knowledge of the oral and parenteral agents used for anticoagulation
- Basic understanding of management strategies with goals for end-stage heart failure and rationale for mechanical circulatory support

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. Circulation 2011;124:e652-e735.
- Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):7S-47S.
- Inotropes and vasopressors review of physiology and clinical use in cardiovascular disease. Circulation 2008;118:1047-56.
- The 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support. Heart Lung Transplant 2013;32:157-87.
- Extracorporeal Life Support Organization (ELSO). General Guidelines for all ECLS Cases [homepage on the Internet].

Table 2-1. Pharmacologic and Risk Factor Recommendations for CABG

Therapeutic or Pharmacologic Domain	Preoperative/Perioperative Recommendations	Postoperative Recommendations/Secondary Prevention
Antiplatelet therapy	• Aspirin preoperatively (or within 6 hr after CABG if not initiated preoperatively) (class I, LOE A) • Doses of 81–325 mg daily (class I, LOE A) • Clopidogrel and ticagrelor should be discontinued ≥ 5 days (class I, LOE B) and prasugrel ≥ 7 days (class I, LOE C) before elective CABG to limit blood transfusions • May be reasonable to perform urgent CABG if clopidogrel or ticagrelor discontinued < 5 days and prasugrel < 7 days (class IIb, LOE C)	• Continue aspirin indefinitely to reduce occurrence of SVG closure and adverse CV events (class I, LOE A) • Higher doses (325 mg) may be preferred to lower doses (81 mg) to prevent aspirin resistance (class IIa, LOE A) • Clopidogrel as alternative if aspirin allergy/intolerance to continue indefinitely (class IIa, LOE C) • After off-pump CABG, dual antiplatelet therapy (aspirin 81–162 mg and clopidogrel 75 mg daily) for 1 yr to reduce graft occlusion (class I, LOE A)
β-Blockers	• Initiate BB perioperatively to prevent POAF and to facilitate BP control; ideally, initiate preoperatively for CABG (class I, LOE A)	• BB for history of MI (class I, LOE A) and/or LV dysfunction (class I, LOE B) • Chronic BB may be considered for HTN in patients with NO MI/LV dysfunction; consider other therapies that may be more effective for HTN (class IIb, LOE B)
Lipids	• Statin preoperatively and reinitiated early postoperatively (class I, LOE A) • Discontinuation of statins should be avoided because adverse reactions can occur (class III, LOE B)	• High-intensity statin (atorvastatin 40–80 mg; rosuvastatin 20–40 mg) for patients < 75 yr (class I, LOE A) • Moderate-intensity statin if intolerant of high-intensity statin or at greater risk of drug-drug interactions (> 75 yr) (class I, LOE A)
ACEIs	• Routine ACEI not recommended early after CABG in the absence of history of MI, LV dysfunction, diabetes mellitus, or CKD (class III, LOE B)	• ACEI for recent MI, LV dysfunction, diabetes mellitus, and CKD (class I, LOE B) • ARB if ACEI intolerant (class I, LOE B)
Blood pressure	• No recommendation	• Reasonable to target goal < 140/85 mm Hg (class IIa, LOE B) • CCB or diuretic as adjuncts if goal not achieved, despite BB and ACEI as appropriate (e.g., in patients without LV/MI) (class IIa, LOE B) • Alternative antihypertensives long term, other than BB, if no history of MI or LV dysfunction (class IIb, LOE B)
Diabetes mellitus	• Serum glucose goal perioperatively should be ≤ 180 mg/dL while avoiding hypoglycemia (class I, LOE B) • Use of continuous IV insulin to achieve the above goal, to reduce the incidence of adverse events such as deep sternal wound infection (class I, LOE B)	• A1C goal < 7% is reasonable to reduce microvascular and macrovascular complications (class IIa, LOE B)
Smoking cessation	• No recommendation	• Smoking cessation is critical; counseling should be offered (class I, LOE A) • Nicotine replacement therapy, bupropion, and/or varenicline as adjuncts are reasonable for stable patients after discharge (class IIa, LOE B) or during hospitalization on an individualized basis (class IIb, LOE B)

(*continued*)

Table 2-1. (*Continued*)

Therapeutic or Pharmacologic Domain	Preoperative/Perioperative Recommendations	Postoperative Recommendations/Secondary Prevention
Mediastinitis/ perioperative infection management	• Preoperative antibiotics to reduce the risk of postoperative infection (class I, LOE A) • A first- or second-generation cephalosporin is recommended in the absence of MRSA colonization (class I, LOE A) • Vancomycin alone or in combination for proven or suspected MRSA colonization (class I, LOE A)	• No recommendation

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blocker; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CKD = chronic kidney disease; CV = cardiovascular; HTN = hypertension; IV = intravenous(ly); LOE = level of evidence; LV = left ventricular; MI = myocardial infarction; MRSA = methicillin-resistant *Staphylococcus aureus*; POAF = postoperative atrial fibrillation; SVG = saphenous vein graft.

Information from: Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary. Circulation 2011;124:2610-42; and Kulik A, Ruel M, Jneid H, et al. Secondary prevention after coronary artery bypass graft surgery. Circulation 2015;131:927-64.

this setting are lacking, and some authors have questioned whether advances in surgical revascularization may limit the ability to detect a significant impact of β-blockers on outcome (Brinkman 2011). Many patients who undergo CABG have strong indications for β-blocker treatment, including hypertension and atrial fibrillation (AF). Furthermore, the risk of AF after CABG is particularly high (Kulik 2015). β-Blockers are highly effective at preventing AF after CABG and at controlling heart rate when it does occur. In addition, continuing β-blockade soon after surgery can help minimize the potential for rebound tachycardia. For these reasons, guideline recommendations continue to support the benefit-risk profile of β-blocker use in the perioperative setting.

MANAGEMENT OF MECHANICAL CIRCULATORY SUPPORT

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is an invasive temporary artificial support for cardiopulmonary failure refractory to conventional therapies. Goals of therapy and type of support required dictate the surgical cannulation approach for the ECMO circuit placement. Venovenous cannulation (i.e., VV-ECMO) removes blood from venous circulation, provides extracorporeal oxygenation and carbon dioxide removal, returns blood to venous circulation, and uses the patient's intrinsic cardiac function, in turn providing only pulmonary support. In general, it is indicated for refractory hypoxic respiratory failure from a variety of causes because it provides only gas exchange without hemodynamic support. Venoarterial cannulation (i.e., VA-ECMO) similarly removes blood from venous circulation but returns blood to arterial circulation, in turn providing cardiac support, with the ability to additionally provide pulmonary support in the form of gas exchange. Indications for VA-ECMO are generally considered severe refractory cardiogenic shock or cardiopulmonary failure. Both VV-ECMO and VA-ECMO are temporary measures to bridge patients to recovery or more permanent intervention.

Anticoagulation

During ECMO, blood is exposed to the foreign surfaces of the ECMO circuit, including the cannulas and oxygenator. Because of blood exposure to non-endothelial surfaces, an inflammatory and prothrombotic response occurs; therefore, anticoagulation to avoid thrombotic events and oxygenator inefficiency caused by thrombus generation must be strongly considered. Limited outcome data exist to guide anticoagulant goals in adults; hence, anticoagulation management strategies and goals in patients receiving ECMO vary among institutions. Heparin is often used for anticoagulation with ECMO and is generally initiated as a 50- to 100-unit/kg bolus at the time of ECMO cannulation, followed by an initial infusion of 7.5–20 units/kg/hour (Lequier 2014). Heparin may temporarily be withheld for several hours in patients immediately after cardiac surgery or those with significant bleeding, but it may rarely require prolonged avoidance in those with ongoing life-threatening bleeding, depending on individualized risk-benefit considerations. During ECMO weaning (i.e., ECMO flows less than 2 L/minute), adequate anticoagulation is essential to avoid circuit thrombosis at lower flow rates.

Methods for assessing the degree of anticoagulation in patients receiving ECMO vary, with no standardized protocol, and may involve monitoring activated clotting time (ACT) only, activated partial thromboplastin time (aPTT) only, a combination of

aPTT and ACT, anti-factor Xa (anti-Xa) activity levels, thromboelastography (TEG), or rotational thromboelastometry (ROTEM). Because ACT is the most common anticoagulation monitoring parameter used for cardiopulmonary bypass (CBP), given its availability as a point-of-care test in the operating room, it has been suggested for monitoring heparin anticoagulation in ECMO. In general, much higher ACTs of 400–480 seconds are targeted for cardiopulmonary bypass (CPB) instead of the commonly accepted goal ACT of 180–220 seconds for ECMO. However, the utility of ACT can be affected by various dynamic hematologic disorders (e.g., anemia, thrombocytopenia, hypofibrinogenemia), making it less than ideal in some situations.

Often, aPTT is used to monitor the effects of heparin outside the operating room and can be used in patients receiving ECMO. Therapeutic ranges differ between laboratories because of the variable response of aPTT reagents to heparin, but aPTT is often targeted to 1.5–2.5 times baseline.

Anti-Xa assays for monitoring heparin in pediatric patients receiving ECMO have shown improved correlation with heparin dose compared with ACT and aPTT and are increasingly used for patients receiving ECMO (Liveris 2014; Bembea 2013). As opposed to measuring actual heparin concentrations, anti-Xa assays monitor the effect of heparin according to its ability to activate antithrombin (AT) to inhibit factor Xa. The advantage of anti-Xa assays over aPTT and ACT is that they are not affected by inherent coagulopathy, thrombocytopenia, or hemodilution. However, some laboratories add exogenous AT to their anti-Xa assays; this is not preferred because of the inherent potential for endogenous AT deficiency in patients requiring ECMO. Laboratories that do not add exogenous AT to their anti-Xa assays depend on the patient's in vivo AT activity and are therefore preferred. Most centers that use anti-Xa concentrations for monitoring heparin anticoagulation in ECMO target goal concentrations of 0.3–0.7 IU/mL, which correlates to an aPTT of 1.5–2.5 times baseline.

Finally, TEG and ROTEM, which are viscoelastic blood tests that show the entire hemostatic process and depict thrombosis dynamics, are additional options in the monitoring of anticoagulant therapy in ECMO. Although TEG and ROTEM provide very similar information, they have slightly different technical processes for obtaining results. The TEG/ROTEM can describe different phases of coagulation and potentially identify sources of coagulation abnormalities such as clot formation, platelet function, clot strength, and fibrinolysis. Use of TEG/ROTEM with heparinase (inactivates the effects of heparin in a blood sample) can help identify underlying coagulation abnormalities in patients receiving heparin. Comparing TEG/ROTEM with heparinase with a non-heparinase TEG/ROTEM can show the effects of heparin by evaluating the differences in R values for TEG or clotting time for ROTEM (Esper 2014; Lequier 2014). When interpreting TEG/ROTEM, R values or clotting time shows the reaction time from when whole blood is placed in the analyzer to the beginning of fibrin formation and depends on coagulation factor availability. Availability and expertise in interpreting TEG/ROTEM limit its use in certain clinical settings. All of the earlier approaches remain viable options for monitoring anticoagulation during ECMO, with various advantages and disadvantages. Additional studies are needed to further define the optimal anticoagulant strategies for such patients.

An additional consideration regarding anticoagulation with heparin during ECMO is the potential need for AT replacement. Heparin relies on AT to exert its anticoagulant effects, and AT concentrations decrease with initiation of ECMO, which can lead to decreased heparin responsiveness or heparin resistance (Esper 2014). Practice with respect to monitoring and replacing AT varies greatly among centers and patient populations (Bembea 2013). Infants have lower relative concentrations of AT than adults and may therefore require replacement more often than adults.

Optimal AT concentrations and consensus on the use of AT to enhance anticoagulation in adult patients receiving ECMO have not been established, but programs using AT concentrations typically target 80%–120% (minimal acceptable concentrations may range from greater than 50% to greater than 100%, depending on the institution), whereas many others do not routinely monitor or replace AT. Patients determined to have AT deficiency, either because of suboptimal AT concentrations or because of heparin resistance, as evidenced by escalating heparin doses (greater than 35–40 units/kg/hour) without adequate response, may benefit from AT supplementation.

Antithrombin can be replaced with AT concentrates or fresh frozen plasma that contains about 1 unit of AT per milliliter for milder deficiencies (Lequier 2014). In patients with profound AT deficiency, AT supplementation generally results in an abrupt and significant reduction in heparin dose requirements, and empiric dose reductions should be considered, together with close monitoring to avoid bleeding. However, in patients with less profound AT deficiency, dose reduction requirements may be much less significant.

Pharmacokinetic Implications

The impact of ECMO on pharmacokinetics is an important consideration that may alter choice of therapy and dosing strategies. In general, drugs administered to patients receiving ECMO support have a larger volume of distribution (Vd) and potentially altered elimination. Often, clearance is reduced in patients receiving ECMO because of associated end-organ dysfunction; however, others who maintain adequate organ function may have an effective increased clearance because of ECMO-related factors. Such factors may include inactivation, sequestration, or adsorption of medications by various components of the ECMO circuit (Shekar 2012a, 2012b, 2012c; Mehta 2007). Much of the data surrounding pharmacokinetics in ECMO have been extrapolated from pediatric and neonatal studies or ex vivo data; published studies regarding the effects of ECMO on pharmacokinetic parameters in adults are scant.

Critically ill patients requiring ECMO are often described as having increased sedation requirements. This may partly be the result of deeper sedation goals (e.g., to avoid inadvertent decannulation, avoid inappropriate movement if the patient has an open chest, improve oxygenation in severe refractory hypoxemia), but it is likely also associated with the pharmacokinetic impact of ECMO on drugs. Ex vivo data show that clinically significant drug sequestration occurs in the ECMO circuit for certain analgesic, sedative, and antibiotic medications, as measured by drug recovery after 24 hours. Average drug recovery of fentanyl from blood samples after 24 hours of exposure to an ECMO circuit primed with blood was 3% compared with 82% recovery in controls, whereas other data indicate 87%–100% of fentanyl was lost after 24 hours of exposure to the ECMO circuit. Although sequestration was not as extensive, clinically significant decreases in serum concentration are also described for midazolam, meropenem, and voriconazole (Shekar 2012b; Mehta 2007).

These ex vivo data are supported by a small retrospective review of analgesia and sedation in 30 adult patients in which a significant increase in dose requirements was suggested for morphine and midazolam during ECMO. In particular, patients on VV-ECMO received higher sedative doses than did patients on VA-ECMO (Shekar 2012c). In general, lipophilic drugs (e.g., fentanyl, midazolam, fluoroquinolones) and highly protein-bound drugs (e.g., ceftriaxone, caspofungin) are more significantly affected by sequestration in the circuit and may warrant close monitoring or the use of alternative agents (Shekar 2015, 2012a).

Vancomycin, a hydrophilic molecule, is minimally sequestered in the ECMO circuit but may have a larger Vd in patients receiving ECMO (Shekar 2012a, 2012b). Data are insufficient to support specific recommendations for modifying therapy in patients receiving ECMO, but patients should be monitored for therapeutic failure when receiving agents thought to be affected by ECMO, and therapeutic drug monitoring should be used, when applicable.

Left Ventricular Assist Device

Use of mechanical circulatory support (MCS) has continued to grow significantly in recent years because of an aging population, increased diagnosis of heart failure, and improved technology. Over 15,000 MCS devices have been implanted since 2006, with more than 2000 devices implanted annually (Kirklin 2015). In end-stage heart failure, heart transplantation is the gold standard treatment in viable candidates, but limited donor availability may make MCS devices a more viable option in such patients.

Patient-specific factors such as heart failure etiology, comorbidities, prognosis, and psychosocial risk factors, among other considerations, will affect the goals and duration of MCS implantation as well as the devices used. In general, the goals of implantation can be categorized as follows: bridge-to-transplantation for transplant candidates to improve functionality and life expectancy while awaiting cardiac transplantation, destination therapy for nontransplant candidates, and bridge-to-decision or bridge-to-recovery for those in whom prognosis or transplant candidacy is not fully elucidated or recovery is feasible. The only formally recognized designations are bridge-to-transplantation and destination therapy, and recovery has only been reported in about 1% of patients after left ventricular assist device (LVAD) implantation (Kirklin 2015).

According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), more than 90% of patients receiving an MCS device have received an LVAD with continuous-flow technology, with most receiving a pulsatile-flow device before 2009. Of the 5111 patients registered in INTERMACS as undergoing LVAD implantation in 2013–2014, 73% received axial continuous-flow LVADs, 26% received centrifugal continuous-flow LVADs, and 1% received pulsatile-flow LVADs (Kirklin 2015). The predominant pumps used are the HeartMate II axial-flow pump (Thoratec, Pleasanton, CA) and the HeartWare HVAD centrifugal-flow pump (HeartWare International, Framingham, MA).

Hemodynamic Management

Hemodynamic treatment of patients with an LVAD differs from that of other populations because of the difference in continuous flow versus pulsatile flow, which often requires invasive monitoring to accurately guide hemodynamic support. Typical pulse pressures in patients with an LVAD are significantly lower than normal (often as low as 10 mm Hg), depending on residual left ventricular functionality, and can be difficult to palpate. In patients with residual left ventricular function, cardiac output (CO) is a combination of LVAD pump flows and left ventricular output, whereas total output in those with minimal left ventricular function more closely correlates with pump flows. In such patients with minimal residual function, aortic valve opening may be sporadic or absent. If possible, cardiac index (CI) goals should be greater than 2.2 L/minute/m^2 and mixed venous saturation goals greater than 60%. Target mean arterial pressure (MAP) is generally 70–90 mm Hg, but it is common to tolerate MAP as low as 60 mm Hg if signs of adequate end-organ perfusion are maintained (Feldman 2013). Often, lower MAP targets can allow decreased afterload to improve pump output. Pharmacologic approaches to optimize postoperative hemodynamics balance CI targets and MAP goals, together with consideration for residual intrinsic LV function (Figure 2-1).

After LVAD implantation, immediate hemodynamic management goals should focus on optimizing right ventricular (RV) function and ensuring adequate end-organ perfusion because the left ventricular function is being supported by the device. The output of LVAD pumps depends on several factors, including blood delivery from the right side of the heart. Patients with baseline RV dysfunction may require diuretics, inotropes, and pulmonary vasodilators with or without mechanical RV support to optimize output. However, RV failure after LVAD implantation may be difficult to predict

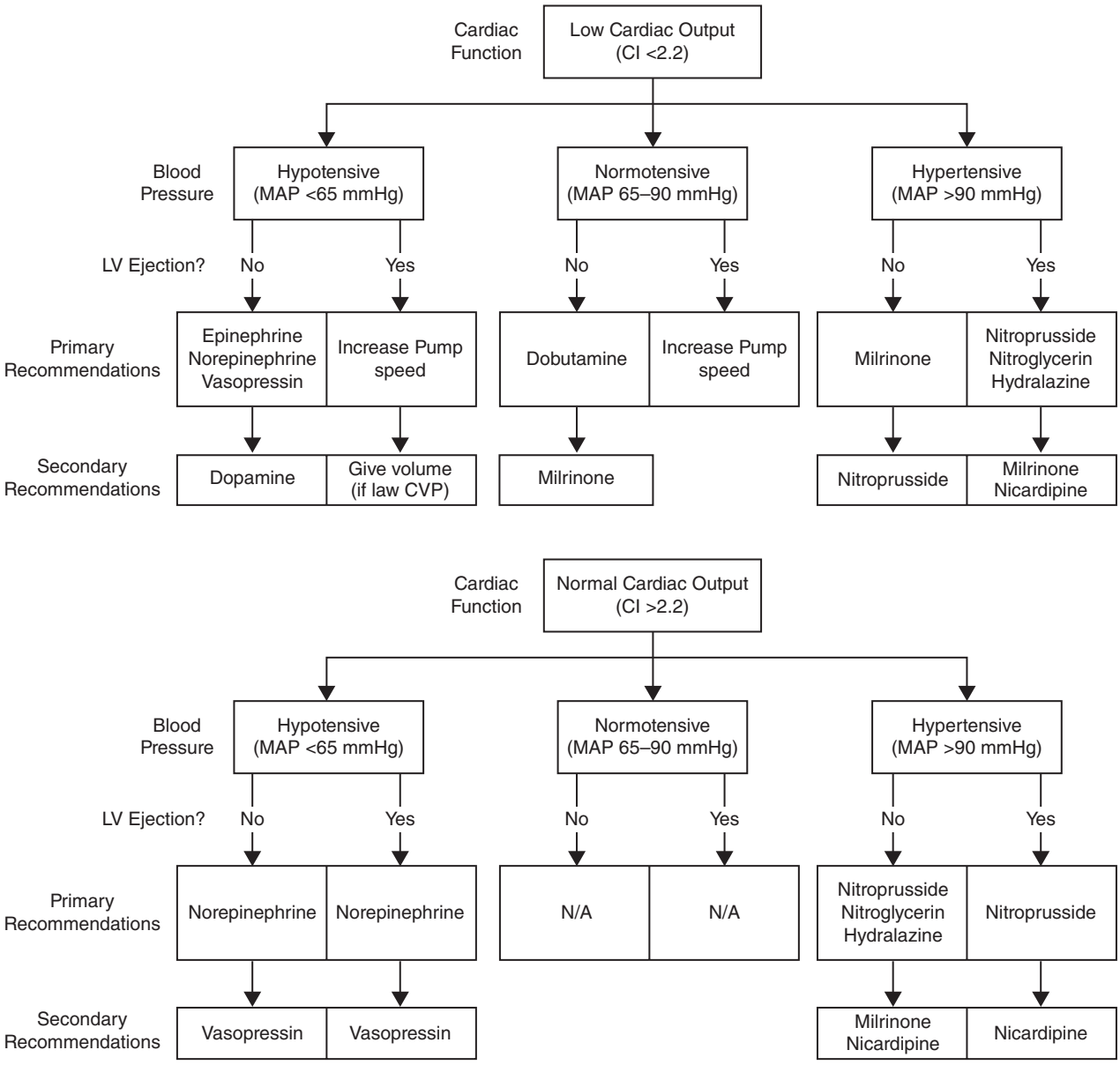

Figure 2-1. Hemodynamic management after left ventricular assist device implantation.

CI = cardiac index; CVP = central venous pressure; LV = left ventricle; MAP = mean arterial pressure; N/A = not applicable.

Information from: Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.

because of postoperative changes in cardiac geometry. As the left ventricle is unloaded, leftward septal shifting results in increased RV volumes and potentially decreased RV contractility. In addition, an increase in venous return from improved CO together with sustained elevated pulmonary pressures can further contribute to RV failure (Pratt 2014).

Central venous pressure (CVP) can be a useful indicator of RV function and must be balanced to ensure adequate preload while avoiding right heart overload. Central venous pressure targets are often patient-specific but are typically 4–14 mm Hg in patients with RV dysfunction. A CVP greater than 18 mm Hg or fluctuation of greater than 4 mm Hg should be evaluated for new or worsening RV dysfunction (Feldman 2013). Interpretation of CVP in combination with other hemodynamic parameters in the setting of low pump output can be useful in determining the causes of a low output state (Table 2-2). Management of RV dysfunction with inotropes and inhaled pulmonary vasodilators is discussed later in this chapter.

Table 2-2. Treatment for Low Pump Output in Patients with an LV Assist Device[a]

CVP	↓	↑	↑	↑	↑
PAP	↓	↓	↑ or ↔	↑	↑
PAOP	↓	↓	↓	↑	↑
MAP	↓	↓	↓	↓	↓
Echocardiography	Underfilled	RV compression	RV/RA dilation	LV/LA dilated, AV opening, inflow malposition	LV/LA dilated, AV opening
Diagnosis	**Hypovolemia or obstruction**	**Tamponade**	**Right heart failure**	**Inflow obstruction**	**Outflow obstruction**
Treatment	**If Hgb < 10 g/dL:** Assess ongoing bleeding and transfuse PRBC **If Hgb > 10 g/dL:** Administer colloid	Emergency surgical intervention	**Target goal CI > 2.2 and CVP 4–14** ↑ PVR & ↑ MAP: SNP or iNO, or iEPO; then milrinone or dobutamine; then implant temporary RVAD ↑ PVR & ↓ MAP: Milrinone or dobutamine, followed by SNP or NTG; then implant temporary RVAD	Requires surgical intervention	Requires surgical intervention

[a]This algorithm should be followed for evaluating and treating low pump output states unrelated to speed or rate of pump. Inflow obstruction and outflow obstruction are rare to very rare.

AV = aortic valve; CI = cardiac index; iEPO = inhaled epoprostenol; iNO = inhaled nitric oxide; LA = left atrium; LV = left ventricle; NTG = nitroglycerin; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PRBC = packed red blood cell; PVR = pulmonary vascular resistance; RA = right atrium; RV = right ventricle; RVAD = right ventricular assist device; SNP = sodium nitroprusside.

Information from: Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.

Antithrombotic Therapies

Early postoperative antithrombotic management after LVAD implantation must be carefully balanced with the risk and management of bleeding. Postoperative anticoagulant strategies and long-term anticoagulant goals have been modified in recent years as experience grows and new evidence emerges. Ultimately, anticoagulant goals and approaches are guided by individual device manufacturers and are institution-specific.

The International Society for Heart and Lung Transplantation guidelines for MCS provide device-specific guidelines for patients able to receive heparin. Recommended early postoperative anticoagulation in patients receiving a HeartMate II device is as follows: complete heparin reversal at the end of surgery after CBP, consider aspirin at ICU admission up to 24 hours postoperatively, initiate intravenous heparin with a goal PTT of 40–60 seconds on postoperative day 1 or 2 if there is no evidence of bleeding (or goal PTT 60–75 if another indication for anticoagulation), and initiate warfarin with an initial goal INR of 1.5–2.5 and aspirin (81–325 mg) on postoperative day 2 or 3. Long-term anticoagulation for the HeartMate II LVAD recommends an INR goal of 2.0–3.0.

Anticoagulation for centrifugal-flow LVADs (i.e., HeartWare HVAD) is very similar and includes comparable recommendations at the end of surgery up to 24 hours postoperatively and a goal PTT of 40–60 seconds on postoperative day 1 or 2, with heparin continued to an eventual goal of PTT 60–80 seconds and initiation of warfarin on postoperative day 2 or 3 with an INR goal of 2.0–3.0 (Feldman 2013). The PTT goals may slightly differ from manufacturer recommendations because of institutional variations in PTT reference ranges.

No clear recommendations exist for antiplatelet regimens after LVAD implantation. Aspirin is most commonly used, though experience has also been reported with dipyridamole and clopidogrel. No consensus exists for antiplatelet agent, dose, or monitoring. Newer antiplatelet agents (e.g., prasugrel, ticagrelor) have not been studied in patients with MCS and are therefore not recommended. Some institutions use platelet monitoring (e.g., platelet aggregation studies, TEG) to guide antiplatelet therapy dosing to the desired level of platelet inhibition (Feldman 2013). The starting dose for aspirin is 81–325 mg, with many institutions routinely starting aspirin 325 mg specifically in HeartWare HVADs because of the increased risk of cerebrovascular events at aspirin doses of 81 mg or lower (Teuteberg 2015).

PERIOPERATIVE MANAGEMENT IN VASCULAR SURGERY

Vascular surgery patients are at very high risk of perioperative complications because of the presence of systemic atherosclerotic disease, advanced age, and commonly extensive comorbidities. Despite the development of less invasive endovascular surgical approaches to minimize intra- and perioperative risks, many patients still require more invasive open procedures, and all patients remain at risk of complications.

Aortic Aneurysm

Description of aortic aneurysm is based on the location and extent of aortic involvement. In general, thoracoabdominal aortic aneurysms (TAAAs) involve aorta distal to the left subclavian artery, extend to the abdominal aorta, and may involve various visceral arteries. Repair of TAAAs is classified by the Crawford classification system and is based on the extent of aortic involvement (Coselli 2007). Abdominal aortic aneurysms (AAAs) involve diseased aorta limited to the abdomen. Repair of aortic aneurysms can be done by an invasive open approach or a less invasive endovascular approach, depending on patient risk factors and surgical feasibility. Although endovascular repair of TAAAs and AAAs has been associated with decreased morbidity and mortality, both open and endovascular surgical approaches carry risk of complications (Lederle 2012; Coady 2010). Common postoperative complications include pulmonary, renal, neurologic, cardiac, and GI. Complications often result from hypoperfusion related to intra- or postoperative hypotension or necessary surgical techniques (e.g., suprarenal aortic cross-clamp approach during surgery resulting in temporary interruption of renal perfusion).

Management and Prevention of Spinal Cord Ischemia

Although rare, spinal cord ischemia is the most significant complication associated with surgical repair of aortic aneurysms and can result in permanent paraplegia. Many preoperative risk factors for spinal cord ischemia are nonmodifiable, including extent of aortic involvement, aortic dissection presentation, and emergency surgery. Additional intraoperative risk factors include duration of cross-clamp time and intraoperative hypotension.

Postoperative strategies are used to help prevent spinal cord ischemia; this results from inadequate perfusion to the anterior spinal cord, normally accomplished by a single vessel, the artery of Adamkiewicz. Spinal cord perfusion pressure is determined by the difference between MAP and CSF pressure (i.e., SCPP = MAP − CSF pressure). The focus of postoperative strategies is to increase oxygen delivery to the spinal cord by optimizing CO, hemoglobin, and spinal cord perfusion pressure. Spinal cord perfusion pressure is optimized by simultaneously decreasing CSF pressure and maintaining elevated MAP. Cerebrospinal fluid pressure can be decreased by placing a lumbar CSF drain, which is generally placed pre- or intraoperatively and maintained for up to 72 hours or longer postoperatively. Drainage pressure can be adjusted in response to clinical signs of lower extremity neurologic deficits, which often manifest as loss of motor function as well as loss of pain and temperature sensation. Conversely, spinal cord perfusion pressure can also be increased by permissive hypertension or afterload augmentation with vasopressors. Norepinephrine, phenylephrine, and/or vasopressin can be used to target a goal MAP of 90–100 mm Hg after other parameters have been optimized (Crimi 2014).

Risk and Management of Perioperative Cardiac Complications

Patients requiring vascular surgery are at high risk of perioperative cardiac complications because of a high prevalence of comorbid CAD and other cardiovascular comorbidities. Patients with an AAA have an estimated 15% risk of cardiac complications. Almost 40% of patients undergoing carotid endarterectomy for carotid artery stenosis also have a diagnosis of symptomatic CAD and atherosclerosis associated with peripheral arterial disease, which is often generalized and commonly associated with CAD (Crimi 2014). Patients should be monitored for risk of MI, ventricular dysfunction, and postoperative atrial fibrillation (POAF). Postoperative hypertension and tachycardia can compromise suture lines after aneurysm repair as well as increase myocardial oxygen demand, resulting in an increased risk of myocardial ischemia and ventricular dysfunction. Early postoperative MI may be associated with embolism of atherosclerotic plaque, whereas delayed MI is often the result of an imbalance between myocardial oxygen supply and demand because of high perioperative stress. Therefore, close monitoring and strict control of blood pressure is imperative to reduce complications and avoid the end-organ dysfunction associated with prolonged hypotension. Electrocardiographic monitoring and evaluation of cardiac biomarkers should be routinely monitored in postoperative vascular surgery patients at risk of cardiac complications. When myocardial ischemia is suspected, aggressive treatment consistent with standard acute coronary syndrome treatment regimens (e.g., β-blockers,

antiplatelet drugs, statins, analgesia) should be initiated as appropriate. Routine use of β-blockers after vascular surgery for preventing cardiovascular events, including MI and postoperative arrhythmia, is also beneficial.

Thrombolytic Therapy for Acute Limb Ischemia

Acute limb ischemia occurs when a sudden decrease or loss in blood flow threatens the viability of an extremity; it is usually a result of thrombosis or embolism. Patients presenting within 2 weeks of symptom onset are considered acute, with rapid diagnosis and treatment crucial to salvaging the ischemic extremity. Depending on patient-specific factors, options for reperfusion include intra-arterial catheter-directed thrombolysis (CDT) and surgical revascularization techniques such as bypass or thrombectomy. Patients with profound limb ischemia may not tolerate the time it takes to achieve effective thrombolysis (i.e., 6–72 hours) and therefore may need urgent surgical revascularization. Catheter-directed thrombolysis offers a comparably effective, low-risk alternative to surgery in mild to moderate limb ischemia, particularly for patients with severe comorbidities who may not tolerate open surgery or those with an extensive history of many surgical or endovascular interventions (Hirsch 2006). Although CDT presents a lower risk of bleeding than historical approaches of systemically administered thrombolytics, CDT may be contraindicated in patients at high risk of bleeding, including those with recent surgery or stroke and those with active bleeding.

Regardless of reperfusion strategy plans, early initiation of systemic anticoagulation with heparin is recommended in patients with acute limb ischemia secondary to arterial emboli or thrombosis to reduce clot propagation and minimize ischemic injury (Alonso-Coello 2012). Choice of thrombolytic agent is largely institution-specific. Despite earlier evidence, use of streptokinase has shifted to primarily guideline-endorsed urokinase or alteplase (tissue plasminogen activator [tPA]) because of decreased efficacy (Alonso-Coello 2012). In some cases, tenecteplase or reteplase may also be used, though many institutions prefer alteplase for use in CDT because of its higher affinity and specificity for plasminogen activation in the presence of fibrin and evidence of faster thrombus dissolution (Robertson 2013; Hirsch 2006). The standard regimen of tPA for CDT is usually an initial bolus of 5–10 mg followed by an intraoperative continuous infusion of 0.5–1.5 mg/hour with initiation. The typical regimen for urokinase in CDT is 4000 units/minute intra-arterially for about 4 hours, followed by 1000–2000 units/minute until the end of lysis. Because of the potential for fibrinogen depletion associated with thrombolytic administration, fibrinogen concentrations should be monitored throughout administration and the infusion adjusted if they fall below 120–150 mg/dL (Walker 2009).

Catheter-directed thrombolysis is often accompanied by low-dose heparin administered through the sheath to maintain patency, or low-dose systemic heparin. In general, full systemic anticoagulation is held until several hours after cessation of thrombolytic therapy when the associated risk of bleeding is reduced.

PERIOPERATIVE COMPLICATIONS AND CONSIDERATIONS

Postoperative Atrial Fibrillation

Atrial fibrillation is the most common postoperative complication of cardiothoracic surgery, with an estimated incidence of 25%–50% (January 2014; Echahidi 2008). The incidence after isolated CABG is about 30%; after valve replacements or repair whereas it is 40%; and for combined CABG and valve procedures it approaches 50%. Postoperative atrial fibrillation usually manifests within 2–4 days after the procedure and peaks on postoperative day 2 (Echahidi 2008). Although this complication is generally transient and manageable in the acute setting, it can portend life-threatening complications including stroke and increased mortality (Echahidi 2008; Almassi 1997; Mathew 1996). Furthermore, the development of POAF after CABG is associated with significant increases in resource use (i.e., increase in length of stay by 1.4 days, higher total postoperative charges per patient, more days of required mechanical ventilation and oxygen therapy, and higher rates of ICU readmission) (Hravnak 2002).

The mechanisms of POAF are multifactorial, but advanced age is the most consistent risk factor (January 2014). Consequently, the overall incidence of this complication is expected to increase substantially with the number of older adult patients undergoing these procedures. Additional risk factors encountered in the cardiothoracic surgical setting that predispose patients to POAF include history of AF, male sex, lower ejection fraction, left atrial enlargement, valvular surgery, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, rheumatic heart disease, and obesity. Each of these risk factors contributes to changes in cardiac structure that predispose to atrial electrical reentry. In addition, physiologic changes because of the surgery itself may increase susceptibility to AF (e.g., atrial incision, perioperative ischemia). Nonetheless, putative mechanisms for POAF involve pericardial inflammation, catecholamine excess, autonomic imbalance, and alterations in volume, pressure, and other neurohormonal mediators. These changes affect the electrical milieu, leading to alterations in atrial refractoriness, slowing of atrial conduction, and formation of multiple reentry wavelets (Echahidi 2008).

Therapeutic strategies to manage POAF involve both prevention and treatment. Several agents have been investigated for their propensity to decrease inflammation and/or modulate both the sympathetic and parasympathetic nervous systems. The 2014 guideline updates endorsed by the American Heart Association/American College of Cardiology/Heart Rhythm Society address evidence-based recommendations for AF, including prevention and treatment of POAF. Table 2-3 outlines the pharmacotherapeutic options that have been investigated for either preventing or treating POAF.

Table 2-3. Pharmacotherapy Options for Prevention and Treatment of POAF

Drug	Mechanism	Prevention	Treatment
β-Blockers	↓ sympathetic tone	X	X
Sotalol	↓ sympathetic tone Restore and maintain NSR	X	X
Amiodarone	↓ sympathetic tone Restore and maintain NSR	X	X
Non-dihydropyridine CCBs	↓ sympathetic tone	X	X
Magnesium	Restore hypomagnesemia	X	
Statins	↓ inflammation	X	
N-3 polyunsaturated fatty acids	Antiarrhythmic effects ↓ inflammation	X	
NSAIDs/corticosteroids	↓ inflammation	X	
Colchicine	↓ inflammation	X	

CCBs = calcium channel blockers; NSR = normal sinus rhythm.

Information from: Echahidi N, Pibarot P, O'Hara G, et al. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793-801.

Prevention of POAF

β-Blockers are the agents most extensively studied for preventing POAF and have the strongest evidence for reducing POAF (Echahidi 2008). A meta-analysis of 28 trials (4074 patients) showed a significant reduction in POAF (OR 0.35; 95% CI, 0.26–0.49) (Crystal 2004). Trials included were heterogeneous in design, definitions, and use of specific β-blockers; however, the robust findings in lowering the risk of POAF persisted. Therefore, guidelines endorse perioperative β-blockers to reduce the risk of POAF and to manage control of blood pressure (Kulik 2015).

Sotalol is a β-blocker with potassium channel blocking effects that is classified as a Vaughan-Williams class III antiarrhythmic. Consequently, it is useful for both rate and rhythm control strategies. Its effects on POAF have been extensively studied, and data support its advantages over traditional β-blockers (Echahidi 2008). A meta-analysis of 14 trials (2583 patients) showed a greater reduction in the incidence of POAF with sotalol relative to other β-blockers (OR 0.42; 95% CI, 0.26–0.65) or placebo (Burgess 2006). Current guidelines recommend prophylactic sotalol be considered to reduce the risk of POAF (January 2014).

Amiodarone is another Vaughan-Williams class III antiarrhythmic with multichannel effects, including β- and α-blockade, as well as calcium channel blocking properties. It has also been extensively studied and has shown significant reductions in the risk of POAF, although the timing of initiation and the dosing regimens used varied widely. The PAPABEAR trial randomized about 600 patients to a 13-day perioperative oral amiodarone regimen (10 mg/kg daily given 6 days presurgery through 6 days postsurgery). Overall, the trial results showed a lower incidence of atrial tachyarrhythmias than with placebo (16.1% vs. 29.5%; HR 0.52; 95% CI, 0.34–0.69; p<0.001) and no differences in serious postoperative complications (Mitchell 2005). The effect of amiodarone was independent of the presence of preoperative β-blocker therapy; however, caution is warranted when these therapies are combined. The risk of hypotension and bradycardia may be augmented with amiodarone, particularly when given intravenously or when average daily doses exceed 1 g (Echahidi 2008). Guidelines, however, endorse amiodarone preoperatively as a reasonable strategy to reduce the risk of POAF in high-risk patients (January 2014).

Data on other pharmacologic strategies for the prevention of POAF are more limited, including non-dihydropyridine calcium channel blockers (CCBs), magnesium, statins, N-3 polyunsaturated fatty acids, NSAIDs, corticosteroids, and, more recently, colchicine. The CCBs have been associated with less supraventricular tachyarrhythmia risk, but at the expense of exacerbating low CO and atrioventricular (AV) block. Therefore, CCBs should be used with caution, except perhaps when the patient is at high risk of POAF and has a contraindication to a β-blocker or amiodarone (Echahidi 2008).

The rationale for magnesium as a preventive strategy is based on the prevalence of hypomagnesemia postoperatively after cardiac surgery and its association with POAF. The use of magnesium in this setting reduces POAF to a magnitude similar to other, more common antiarrhythmics (Miller 2005). These trials were relatively small and different in design; hence, the AF guidelines do not specifically address magnesium.

Statins have been associated with lower rates of POAF in observational studies, presumably because of their anti-inflammatory properties. A prospective trial, ARMYDA-3, validated these early findings with about a 60% relative risk reduction in POAF when atorvastatin 40 mg daily was initiated 7 days before elective cardiac surgery and continued postoperatively (Patti 2006). Similar to statins, polyunsaturated fatty acids have been associated with a lower incidence of AF in extensive observational data analyses. A prospective trial of 160 subjects showed a significant reduction in the incidence of POAF (Calo 2005). Neither statins nor polyunsaturated fatty acids, however, are mentioned in the AF guideline recommendations.

Other therapeutic modalities for attenuating inflammation in the perioperative setting that have been investigated for the prevention of POAF include NSAIDs, corticosteroids, and colchicine. Although NSAIDs and corticosteroids have shown some promise in significantly lowering the incidence of POAF, concerns exist about increasing the risk of nephrotoxicity and perioperative bleeding (Echahidi 2008). Colchicine was recently investigated in the COPPS substudy for the prevention of AF (Imazio 2011). In this multicenter trial, the use of colchicine significantly lowered the incidence of POAF at 30 days compared with standard therapy (12% vs. 22%; p=0.021). Subjects in the colchicine arm also had a lower hospital length of stay. Colchicine is therefore included in the AF guidelines as a consideration to reduce POAF (January 2014).

Treatment of POAF

The approach to treating POAF is generally consistent with that of managing AF outside the surgical setting. The initial step is to evaluate for the presence of precipitating factors that can be addressed (i.e., electrolyte disturbances such

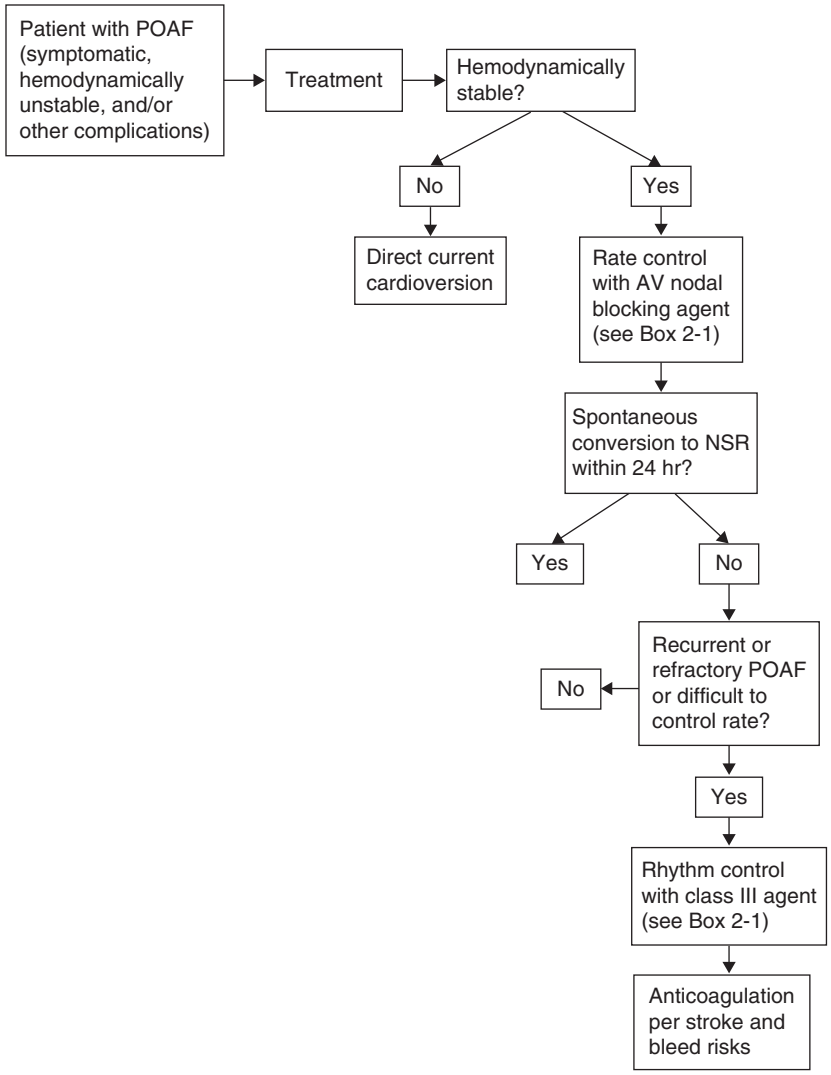

Figure 2-2. Treatment algorithm for postoperative atrial fibrillation.

AV = atrioventricular; NSR = normal sinus rhythm; POAF = postoperative atrial fibrillation.

Box 2-1. Pharmacologic Options for Postoperative Atrial Fibrillation – Example Regimens

Rate Control Options

- Metoprolol 2.5–5 mg IV over 2 min; then 50–100 mg twice daily PO
- Atenolol 1–5 mg IV over 5 min and repeat after 10 min; then 50–100 mg twice daily PO, adjusted for kidney function
- Esmolol 500 mcg/kg IV over 1 min; then 50–200 mcg/kg/min IV infusion
- Diltiazem 0.25 mg/kg IV over 2 min; then 5–15 mg/hr IV infusion
- Verapamil 2.5–10 mg IV over 2 min; then 40–60 mg twice daily PO

Rhythm Control Options

- Amiodarone 150 mg IV; then 0.5–1 mg/min IV infusion; then PO as tolerated
- Ibutilide 1 mg IV over 10 min; may repeat after 10 min if no effect
- Sotalol 80–160 mg twice daily PO, or alternatively, 75–150 mg twice daily IV, adjusted for kidney function

IV = intravenous(ly); PO = oral(ly).

as hypokalemia or hypomagnesemia, volume overload, ischemia, hypoxia). Medical management is then warranted for patients who remain symptomatic, become hemodynamically unstable, or develop complications such as heart failure or ischemia (Echahidi 2008). Like with typical AF management, the decision to use a rate or rhythm control strategy together with anticoagulation must be weighed. A general treatment algorithm for POAF is summarized in Figure 2-2, and pharmacologic options for POAF are summarized in Box 2-1.

In general, attaining effective rate control is an appropriate first choice for hemodynamically stable patients. Although there is no consensus heart rate goal, many trials used an end point of less than 90 or 100 beats/minute. β-Blockers are recommended first line, and non-dihydropyridine CCBs are suitable alternatives (January 2014). Rhythm control with direct current cardioversion should be used whenever the patient is unstable. Providing rhythm control with an antiarrhythmic suited for cardioversion and maintaining normal sinus rhythm should be reserved for patients who have recurrent or refractory POAF or when the ventricular rate is difficult to control. Pharmacologic options for rhythm control include amiodarone, ibutilide, and sotalol. Ibutilide is particularly well suited for chemical cardioversion because of its rapid onset (about 90 minutes) relative to amiodarone. Therefore, it is included in the AF guidelines as an alternative to direct current cardioversion (January 2014). The caveat with ibutilide is that it carries a relatively high risk of polymorphic ventricular tachycardia because of QTc prolongation (3.6%–8.3%), which requires continuous ECG monitoring during administration and for up to 4 hours after the infusion has ended. This risk also exists with the other class III antiarrhythmics used for rhythm control, although the incidence associated with amiodarone is quite low (Bernard 2003). Amiodarone is preferred in patients with left ventricular dysfunction because of its overall effectiveness and safety in this patient population, whereas sotalol may be preferred in patients with CAD (January 2014).

Finally, the decision to initiate anticoagulation for POAF can have consequences. Postoperative atrial fibrillation is associated with a significant excess of strokes. Anticoagulation could presumably reduce this risk, although controlled studies are lacking. In addition, the risk of bleeding with anticoagulation in the perioperative setting may be prohibitive. Anticoagulation is favored when the AF lasts more than 48 hours, when frequent episodes of POAF occur, or in patients with a history of stroke or transient ischemic attack. Conversely, anticoagulation may be best avoided in the patients most susceptible to bleeding (i.e., advanced age, uncontrolled hypertension, and history of bleeding) (Echahidi 2008).

Cardiogenic Shock

Shock is a state of inadequate tissue perfusion and oxygen delivery because of cardiovascular dysfunction. Acute MI is the most common etiology for cardiogenic shock, especially with anterior infarctions and in the presence of multivessel disease (Hollenberg 1999). The mortality rate with cardiogenic shock after an acute MI is around 40%. Data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database show that overall operative mortality was 18.7% among patients with acute MI complicated by cardiogenic shock who underwent CABG (Acharya 2016). Patients who underwent CABG as a salvage procedure or who required MCS had the highest rates of operative mortality (37.2%–58.4%) (Acharya 2016). Other causes of cardiogenic shock encountered in the cardiac surgical setting include mechanical complications of acute MI (i.e., acute mitral regurgitation, rupture of the intraventricular septum, free wall rupture), large RV infarctions leading to RV failure, cardiac dysfunction with prolonged CPB, myocardial contusion, septic shock with severe cardiac depression, valvular heart disease, myocarditis, end-stage cardiomyopathy, and hypertrophic obstructive cardiomyopathy (Hollenberg 1999).

The pharmacologic treatment approach to shock encompasses a variety of vasoactive medications that are categorized according to their predicted effects on cardiac contractility and vascular tone (Figure 2-3). However, the pharmacologic effects of each agent show marked interindividual variability because many factors influence response (i.e., dose, cardiac reserve, underlying disease process, and concomitant drugs).

For patients in cardiogenic shock who have adequate intravascular volume, the initial approach is to restore tissue perfusion with inotropic support until the underlying cause can be addressed. Inotropes can be used to achieve a target CI of 2.2 L/minute/m^2 or greater, but markers of global perfusion may be preferable (i.e., near-normal mixed venous oxygen saturation [Svo_2], normal or declining lactate, urine output greater than

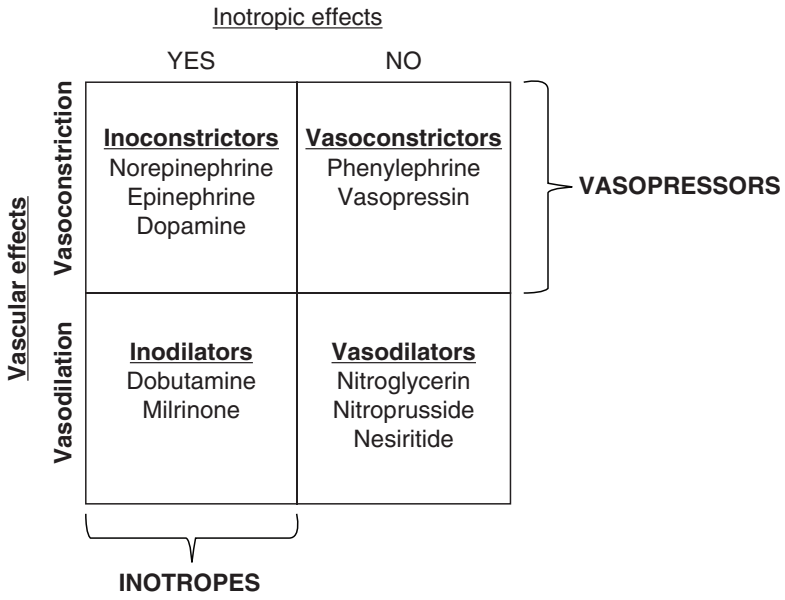

Figure 2-3. Pharmacologic treatment considerations in the management of shock.

0.5 mL/kg/hour) (Hollenberg 2011). Dobutamine and milrinone are inotropic vasodilators ("inodilators") commonly used to treat cardiogenic shock. Each agent increases stroke volume and CO through stimulation of myocardial contractility, together with reduced systemic vascular resistance (afterload) because of systemic vasodilation. An inodilator is preferred to an agent that acts as an inotropic vasoconstrictor (inoconstrictor) because of its more favorable effects on afterload, cardiac filling pressures, and myocardial blood flow (Fowler 1984; Sato 1982).

The primary risks with all of these agents are proarrhythmias and precipitation of myocardial ischemia; however, hypotension is also a concern with the inodilators (Petersen 2008). A subgroup analysis from the SOAP-II trial found significantly greater mortality in patients with cardiogenic shock who received dopamine, together with a doubling of the risk of tachyarrhythmias (De Backer 2010). Other data analyses show similar findings of increased mortality and adverse events in hospitalized patients, underscoring the importance of careful patient selection to those whose CO is inadequate to maintain organ function (Abraham 2005; Cuffe 2002).

Once the decision has been made to initiate inotropic support, an agent is selected on the basis of pharmacokinetic, clinical, and evidence-based factors. Dobutamine is regarded as the preferred inotrope for acutely unstable patients because its rapid onset and short half-life (around 2 minutes) allow for prompt increases in CO. It is also preferred when the systolic blood pressure is less than 100 mm Hg because the vasodilatory effect is less than with milrinone (Jentzer 2015). In certain clinical situations, dobutamine may be less ideal because of its association with the development of tachyphylaxis with β-adrenergic receptor down-regulation and in patients who recently received β-blockers where an impaired response would be seen because of receptor antagonism (Metra 2002).

Unlike dobutamine, milrinone is a phosphodiesterase type 3 (PDE3) inhibitor that augments downstream β-adrenergic receptor signaling and activation, resulting in inotropic and vasodilatory properties. Milrinone retains its inotropic activity and produces sustained hemodynamic effects in patients whose receptors are down-regulated or pharmacologically blocked (Lowes 2001). The stimulation of myocardial contractility is arguably greater with dobutamine, but the pulmonary and systemic vasodilation that occurs with milrinone is more profound (Mager 1991). Milrinone is therefore preferentially used in patients with significant RV dysfunction and pulmonary hypertension (PH) (Eichhorn 1987). The onset of milrinone is much slower than that of dobutamine, with similar hemodynamic effects seen after about 2–3 hours of initiating the maintenance infusion. Loading doses are generally not used because of the risk of hypotension (Hollenberg 2011). In addition, the clearance of milrinone depends on kidney function. Dose reductions for patients with declining kidney function (CrCl less than 50 mL/minute/1.73 m^2) are recommended to minimize drug accumulation and toxicity as the half-life progressively increases from 2–3 hours to up to 4–6 hours or more (Jentzer 2015). Therefore, dobutamine may be more appropriate for patients with acute kidney injury or advanced kidney disease. Despite the differences between agents, clinical efficacy and safety outcomes were similar in hospitalized patients with heart failure who awaited transplantation (Aranda 2003).

Perioperative Hemorrhage

In general, the guidelines recommend a conservative approach to the use of perioperative blood product transfusions. Blood transfusions are a limited resource, are costly, and have the potential for detrimental adverse effects. Therefore, it is necessary to consider strategies to prevent bleeding associated with surgery and minimize blood loss in patients who experience bleeding. Pharmacologic agents play an important role as an adjuvant therapy to reduce or prevent blood loss and the need for allogeneic blood product transfusions.

Prevention of Hemorrhage

Interruption of Antithrombotic Agents Before Nonemergency Surgery

In nonemergencies, consideration should be given to the interruption of antithrombotic agents before surgery. Many factors such as indication for antithrombotic agent, risk of thrombosis, type of surgery, risk of bleeding, pharmacokinetics of the agent, and organ function play a role in the decision whether to interrupt antithrombotic agents before surgery.

Clinical practice guidelines recommend interrupting vitamin K antagonist therapy 5 days before surgery using short-acting parenteral therapy for anticoagulant bridging in patients at high risk of thromboembolism. Stratification of risk of perioperative thromboembolism and the need for perioperative bridging should be individualized to patient-specific scenarios. This involves assessing the $CHADS_2$ score for patients with AF, the position and type of valve for patients with a mechanical heart valve, and the time interval from the index venous thromboembolism (VTE) event to surgery for patients with a history of VTE.

The BRIDGE trial evaluated bridging anticoagulation in patients with AF requiring surgery. Trial data showed that omitting anticoagulant bridging perioperatively was noninferior to bridging with low-molecular-weight heparin for preventing arterial thromboembolism and was associated with a decreased risk of major bleeding. Cardiac surgery patients were excluded from the BRIDGE trial, and most patients in the trial were at low risk of thromboembolism, with a mean $CHADS_2$ score of 2.3 (Douketis 2015). In patients who are deemed at high risk of thromboembolism or who otherwise require heparin or low-molecular-weight heparin for perioperative bridging of anticoagulation, the last preoperative dose of therapeutic low-molecular-weight heparin should be given about 24 hours before surgery (Douketis 2012). Each of the manufacturers' package inserts provide specific recommendations for the timing of discontinuation of the novel oral anticoagulants before surgery (Table 2-4).

Perioperative management of antiplatelet drugs before cardiac surgery can present further challenges. Most patients presenting for cardiac surgery, particularly CABG, are receiving chronic aspirin therapy, which should be continued

Table 2-4. Terminal Half-lives and Manufacturer Recommendations for Holding Direct-Acting Oral Anticoagulants Before Surgery

Medication	Half-life Elimination	Recommendation to Hold Before Surgery	Antidote[a]
Apixaban	~12 hr	Discontinue at least 48 hr before elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding	Andexanet alfa[b]
Dabigatran	12–17 hr	Discontinue 1–2 days (CrCl ≥ 50 mL/min/1.73 m^2) or 3–5 days (CrCl < 50 mL/min/1.73 m^2) before invasive or surgical procedures because of the increased risk of bleeding	Idarucizumab
Edoxaban	10–14 hr	Discontinue at least 24 hr before invasive or surgical procedures because of the risk of bleeding	Andexanet alfa[b]
Rivaroxaban	Healthy adults: 5–9 hr Older adults: 11–13 hr	Should be discontinued at least 24 hr before the procedure to reduce the risk of bleeding	Andexanet alfa[b]

[a]Antidotes should only be used if inadequate time has elapsed since the last dose of direct-acting oral anticoagulant and emergency surgery is imminent.

[b]Andexanet alfa is not currently FDA approved.

Information from Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-24.

until the time of surgery for the prevention of cardiovascular events and resumed within 6 hours after CABG or on hemostasis. Conversely, because of the increased bleeding risk with $P2Y_{12}$ antagonists, it is recommended that clopidogrel and ticagrelor be discontinued 5 days before surgery, whereas prasugrel should be discontinued 7 days before surgery, when possible.

Patients at highest risk of recurrent ischemic events or ongoing ischemia may require an operation before full recovery of platelets after discontinuing $P2Y_{12}$ antagonists. In patients with recent coronary stent placement – generally considered a bare metal stent less than 6 weeks, a drug-eluting stent less than 6 months (potentially sooner after placement of new-generation drug-eluting stents), or otherwise at high risk of stent thrombosis (based on type, location, and number of stents, or ischemic risk and extent of CAD) – bridging with short-acting antiplatelet therapy may be warranted before or during surgery. Bridging strategies have been described for patients at high risk of ischemic events with recent drug-eluting stents, in whom dual antiplatelet therapy must be held, using glycoprotein IIb/IIIa inhibitors or cangrelor (Roffi 2016; Angiolillo 2012; Savonitto 2010). Identification of appropriate patients at increased risk of ischemic events, together with assessment of bleeding risk versus thrombosis risk and consideration of cost, should be conducted before initiating such therapies because evidence in this population is limited.

Reversal of Anticoagulants Before Emergency Surgery

In emergency cardiac surgery, adequate time for interruption of anticoagulant therapy is often not feasible. Such scenarios may necessitate the use of reversal strategies to reduce the bleeding risk associated with surgery in patients receiving anticoagulants. Reversal strategies for anticoagulant therapies continue to evolve from traditional approaches of blood products and vitamin K to emerging agents including prothrombin complex concentrate (PCC) and anticoagulant-specific agents for the reversal of direct-acting oral anticoagulants.

Prothrombin complex concentrates are blood product–derived agents containing various amounts of coagulation factors. Initially, three-factor PCCs, although only indicated for use in patients with hemophilia, were used off-label for warfarin-associated hemorrhage. In recent years, PCCs have increasingly been used for reversing anticoagulation from warfarin, and in 2013, four-factor PCC (4F-PCC) gained FDA label approval for use in warfarin reversal in patients undergoing surgery. In a comparative study of 4F-PCC versus plasma, which has historically been the standard for rapid vitamin K antagonist reversal in patients needing urgent surgical intervention, 4F-PCC was superior to plasma for rapid INR reversal and effective hemostasis. In addition, the authors found no difference in thromboembolic adverse events, but a decrease in fluid overload in patients who received 4F-PCC compared with plasma, highlighting one of the potential advantages of 4F-PCC because of its significantly lower relative volume (Goldstein 2015). In a single-center, retrospective cohort study, conservative-dose 3F-PCC with vitamin K targeting INR reversal to 1.5 or less before surgery was safe and effective in patients before heart transplantation, including in patients with an LVAD (Kantorovich 2015).

Because of their difference in mechanism of action, alternative approaches must be considered for reversing direct-acting oral anticoagulants. Dabigatran, a direct thrombin inhibitor, was the first direct-acting oral anticoagulant approved for use in the United States. Various strategies have been described for reversing dabigatran, with limited success overall. In a study of healthy volunteers, 4F-PCC had no influence on the anticoagulant action of dabigatran (Eerenberg 2011). A case report and data in healthy volunteers, however, show the potential role of factor eight inhibitor bypass activity (FEIBA) for reversing anticoagulant activity and improving hemostasis (Dager 2013; Marlu 2012). Hemodialysis, when feasible considering the urgency of surgery and access, has also been described as a viable option for removing dabigatran before surgery because of its low molecular weight and relatively low protein binding (Wanek 2012; Stangier 2010). In October 2015, idarucizumab, a humanized monoclonal antibody fragment targeted to bind dabigatran, was FDA approved for use in patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery. An interim analysis of a prospective cohort study evaluating the effects of idarucizumab reported that the anticoagulant effects of dabigatran were completely reversed within minutes, and 33 of 36 patients who underwent a procedure had normal intraoperative hemostasis (Pollack 2015). Although this analysis was not without limitations, idarucizumab was associated with a very low incidence of thrombotic events (Pollack 2015).

Reversal strategies for oral factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) differ from those for dabigatran. Hemodialysis has not been shown to be a viable option, but 4F-PCC and FEIBA are both effective in reversing the anticoagulant effects of rivaroxaban (Marlu 2012; Eerenberg 2011). Although options are currently limited, promising results from a study of older healthy volunteers show that andexanet alfa, a specific reversal agent that is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors, may be a viable option in the future, pending FDA approval (Siegal 2015). Ultimately, the risks and benefits of reversal strategies must be weighed against the urgency and risks associated with the surgery.

Pharmacologic Management of Coagulopathy

Profound coagulopathy caused by CPB resulting in massive hemorrhage has been associated with cardiac surgery. Massive hemorrhage requiring surgical reexploration has

historically been reported in as many as 6% of all cardiac surgery cases. Coagulopathy during cardiac surgery is commonly treated with blood products (e.g., fresh frozen plasma, pooled platelets, cryoprecipitate) to replace deficiencies and promote hemostasis. Pharmacologic agents, including antifibrinolytics such as aminocaproic acid and tranexamic acid, can additionally be used to help prevent coagulopathy with cardiac surgery.

In patients with bleeding related to known or suspected platelet dysfunction, desmopressin should be considered; this agent is effective at reducing volume of blood loss. On separation from CPB at the end of surgery, protamine should be given to neutralize the effects of heparin given during CBP. The protamine dose is based on the heparin dose the patient received, using 1.0–1.5 mg of protamine per 100 units of heparin. Despite these common measures to treat and prevent the bleeding associated with cardiac surgery, severe postoperative coagulopathy can occasionally result in bleeding refractory to routine treatment and preventive approaches, circumstances potentially necessitating additional hemostatic agents.

Shortly after 1999, when it received FDA label approval for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors, recombinant activated factor VIIa (rFVIIa) began to be used for off-label indications. In 2000–2008, off-label rFVIIa use in hospitals skyrocketed 143-fold, with adult cardiovascular surgery the most common indication (27% in 2008) for use (Logan 2011). Despite inconsistent evidence of outcome benefits, rFVIIa has often been used in cardiac surgery as a final effort in massive hemorrhage secondary to refractory coagulopathy.

Of particular concern with respect to rFVIIa use is its prothrombotic nature and risk of thromboembolic events. A systematic review of rFVIIa use in cardiac surgery patients found no mortality benefit but an increased risk of thromboembolism (Yank 2011). As such, rFVIIa should be reserved for life-threatening bleeding because of coagulopathy unresponsive to standard blood product transfusion approaches and bleeding unrelated to a surgical source, in which case surgical intervention would be necessary. For patients in whom intractable bleeding may warrant the use of rFVIIa, optimal dosing has not been clearly established. Dosing with earlier use of rFVIIa was often described to be consistent with the recommended dosing for hemophilia of 90 mcg/kg (Romagnoli 2006). However, non-hemophiliac coagulopathies likely do not present the same degree of coagulation impairment seen in hemophilia, and a lower dose should be considered.

The largest randomized prospective study of data on the use of rFVIIa in cardiac surgery found a reduction in reoperation for bleeding and a reduction in the need for transfusions in patients receiving 40 mcg/kg or 80 mcg/kg; however, the study found numerical increases in clinically significant adverse events, including cerebral infarction (Gill 2009). Retrospective data in 62 patients receiving rFVIIa for refractory, life-threatening bleeding associated with LVAD procedures showed that, although laboratory values and transfusion requirements were reduced with rFVIIa, there were significant increases in the incidence of thromboembolic events (36.7% of patients receiving 30–70 mcg/kg, 9.4% of patients receiving 10–20 mcg/kg) (Bruckner 2009).

Because of the high risk of thrombotic events in patients with MCS, rFVIIa should be avoided in this population, even at low doses. Additional propensity-matched data showed that rFVIIa use in cardiac surgery patients was associated with an increased risk of mortality and renal morbidity (Alfirevic 2014). For patients in whom traditional measures for managing coagulopathy have been exhausted and life-threatening hemorrhage persists, the potential risks and benefits of rFVIIa must be evaluated. If potential benefits outweigh risks, conservative rFVIIa dosing may help treat refractory coagulopathy after cardiac surgery in final efforts but mitigate the risk of thromboembolism.

The more recent availability of PCCs has led to a growing interest in their role for the treatment of coagulopathy associated with cardiac surgery. Although perioperative use of PCCs for anticoagulant reversal for emergency surgery has been described, use for treatment of non–drug-induced coagulopathy in the cardiac surgery population is limited.

In a propensity-score matched analysis of 225 pairs of patients for whom 3F-PCC was used as sole first-line treatment for coagulopathy after cardiac surgery instead of fresh frozen plasma, 3F-PCC was associated with decreased postoperative blood loss but an increased risk of postoperative acute kidney injury compared with fresh frozen plasma (Cappabianca 2016). An observational study of 25 cardiac surgery patients with coagulopathy and life-threatening bleeding refractory to conventional therapies reported that FEIBA (1000–4000 units) administered intraoperatively before chest closure resulted in a decreased need for fresh frozen plasma and platelet transfusions, together with no patients requiring reexploration, no operative mortality, and only one thromboembolic event (Song 2014).

Often, coagulopathy during cardiac surgery can be a result of disseminated intravascular coagulation (DIC), in which case PCCs should be avoided because of their procoagulant properties and the risk of thrombotic events in DIC. Interpretation of TEG intraoperatively or postoperatively can assist in identifying the fibrinolytic process associated with DIC and can therefore guide decision-making on the role of PCC. At this time, evidence surrounding the use of PCC for this indication is limited but continues to emerge, and PCC may begin to replace rFVIIa as the pharmacologic agent for treatment of severe refractory bleeding after cardiac surgery.

A nonrandomized retrospective evaluation of 50 patients receiving 3F-PCC compared with 100 patients receiving rFVIIa showed that 3F-PCC was superior with respect to transfusion requirements and cost as second-line treatment

for severe refractory bleeding after complex cardiac surgery (Tanaka 2013). Until further evidence on their safety and efficacy is available, PCCs should likely not be used routinely in such circumstances, but PCCs may be considered in life-threatening bleeding.

Management of RV Dysfunction and PH

Right ventricular dysfunction refers to an abnormality of RV function detected with any test (usually imaging), whereas RV failure is a clinical syndrome of right-sided heart failure usually associated with hemodynamic findings of low CO with high RV filling pressures (Simon 2013). Right ventricular function and LV function are interdependent, and both have essential physiologic functions. The presence of RV failure is therefore associated with worse outcomes, regardless of cause (Simon 2013). The etiologies of RV dysfunction and failure vary widely, but more typical examples encountered in the perioperative setting include cardiomyopathies, congenital disease (i.e., atrial or ventricular septal defect), valvular heart disease (before or after surgical repair), volume overload of the RV, sepsis, and PH (pressure overload of the RV) (Simon 2013).

Secondary causes of PH because of underlying cardiac, pulmonary, or thromboembolic diseases are more commonly seen than pulmonary arterial hypertension (PAH; formerly, primary PH) in the perioperative setting; however, the exact prevalence is uncertain. Other complicating intraoperative factors can worsen PH by causing pulmonary endothelial injury and vasoconstriction (i.e., vasospastic stimuli such as duration of CPB, ischemia-reperfusion injury, acidosis, and other inflammatory mediators) (Fischer 2003). Patients who develop PH in this setting usually have less severe elevations of mean pulmonary artery pressure (PAP) to less than 40 mm Hg but have typical signs and symptoms such as jugular venous distention, peripheral edema, and dyspnea (Fischer 2003). Furthermore, the development of PH in this setting portends a significant increase in the risk of both mortality and perioperative MI (Reich 1999).

The primary approach for RV dysfunction or failure is to treat the underlying cause. Treatment principles focus on reducing RV afterload (pulmonary vascular resistance [PVR]). The basis for this recommendation is that the RV is sensitive to acute increases in PVR, which leads to a significant increase in RV pressure and a lowering of RV ejection fraction. However, systemic pressure (systemic vascular resistance) should be maintained or increased, because this is proportional to RV coronary perfusion pressure (Fischer 2003). The performance of the RV is also influenced by normal sinoatrial and AV conduction. The loss of AV synchrony, as in conditions such as AF, can have detrimental consequences on RV function through the reduction in ventricular filling seen with the loss of atrial "kick." Therefore, restoration of sinus rhythm is imperative.

Supportive therapies to reduce PVR perioperatively include the following: improve oxygenation, avoid respiratory acidosis, correct metabolic acidosis, avoid ventilation/perfusion mismatch, avoid overinflation of lung alveoli, provide adequate sedation and analgesia to minimize catecholamine release, and avoid shivering (Fischer 2003). Specific treatments designed to improve RV dysfunction/failure, whether or not complicated by PH, are summarized in Table 2-5.

Judicious volume management is paramount in all forms of RV failure. Right ventricular preload (CVP) should be optimized such that volume overload and septal shifting leading to impaired LV filling are avoided (Simon 2013). A conservative volume challenge may be warranted if the CVP is less than 10 mm Hg; however, overaggressive volume repletion can be deleterious (Fischer 2003). In these cases, loop diuretics may be required to maintain a patient-specific CVP goal, depending on clinical response. The effectiveness of diuretics in patients with RV failure, however, may be compromised by the presence of intestinal edema, which can impair absorption. Therefore, agents with higher bioavailability (i.e., bumetanide, torsemide) may be required (Cook 1988).

Positive inotropes are recommended for patients with documented or suspected low CO, as evidenced by one or more of the following: cool extremities, impaired mental status, cyanosis, kidney impairment, or impaired response to diuretics (Imazio 2011). In these cases, invasive hemodynamic monitoring may be warranted to confirm low CO and/or to help guide treatment if frequent titrations of inotropes are required.

Both dobutamine and milrinone are clinically effective in patients with low CO and in patients with PH after cardiac surgery (Fischer 2003). The enhanced vasodilatory properties of milrinone make it particularly useful to treat patients with RV failure and PH (Chen 1997). However, caution is warranted because of the risks of hypotension and accumulation in kidney impairment. In these cases, dobutamine is preferred. As an alternative, inhaled milrinone has been described and shown to cause pulmonary vasodilation without systemic hypotensive effects (Fischer 2003).

For patients who do present with marked hypotension and shock, inotropic vasopressors may be required. Norepinephrine has been advocated in this situation because it decreased the ratio of PAP to systemic blood pressure without a change in CI because of its balanced α and β effects (Fischer 2003). For severely reduced CO, epinephrine may be required. However, each of these agents must be used with caution because their potent vasopressor effects may increase the PAP, causing further clinical deterioration (Fischer 2003).

In addition to the supportive therapies required to manage RV dysfunction/failure, patients with evidence of PH commonly require the use of pulmonary vasodilators. These treatments have traditionally included inhaled nitric oxide and epoprostenol, although more recently, PDE inhibitors have been used. The evidence base for these therapies is most robust in patients with PAH. However, these therapies have been studied as adjunct treatments for acute RV dysfunction complicating cardiac surgery (Griffiths 2005).

Table 2-5. Treatments for RV Failure

Class of Medication	Mechanism	Clinical Pearls
Loop diuretics • Furosemide, bumetanide, torsemide	• Relieve RV volume overload	• Kidney function in the setting of RV failure may improve with diuresis (in the setting of high venous filling pressures) • Bumetanide/torsemide may be preferable to furosemide because of its enhanced bioavailability
Inotropes • Dobutamine, milrinone	• Improve RV function and augment CO	• Milrinone is especially suited to the treatment of RV failure complicated by PH because of its pulmonary vasodilator effects
Inhaled nitric oxide	• Acute pulmonary vasodilator • Reduces PVR • Improves oxygenation	• Pulmonary selectivity by inhalation route • Acute benefits only • Benefits seen in ARDS with most severe hypoxemia
Prostacyclins • Epoprostenol	• Pulmonary vasodilator • Reduces RV afterload and improves RV function • Induces reverse remodeling of pulmonary vasculature	• Primary indication is for PAH • Caution with PH caused by pulmonary venous congestion/LV dysfunction (pulmonary edema) and PH caused by hypoxic lung disease (V/Q mismatch)
PDE5 inhibitors • Sildenafil	• Pulmonary vasodilator • Reduces RV afterload and improves RV function	• Primary indication is for PAH • Caution with PH caused by pulmonary venous congestion/LV dysfunction (pulmonary edema) and PH caused by hypoxic lung disease (V/Q mismatch)

ARDS = acute respiratory distress syndrome; CO = cardiac output; LV = left ventricular; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type-5; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RV = right ventricular; V/Q = ventilation/perfusion ratio.

Inhaled nitric oxide and epoprostenol are potent pulmonary vasodilators that have acutely improved hemodynamics through reductions in both PVR and PAP, as well as improvements in oxygenation. Thus, they are useful short-term adjuncts in patients with PH in the perioperative setting (Solina 2001; Pepke-Zaba 1991). Inhaled nitric oxide has been evaluated over a range of doses (10–40 ppm); however, some data analyses show that doses exceeding 10 ppm were not associated with greater reductions in PVR (Solina 2001). The pulmonary selectivity of inhaled nitric oxide is an advantage over epoprostenol; however, the delivery system and costs associated with inhaled nitric oxide (particularly in the adult patient, for whom it lacks FDA label approval) limit its widespread use (Fischer 2003). Dose-dependent inhaled nitric oxide toxicity and adverse events such as methemoglobinemia and increased bleeding time have also been reported (Fischer 2003). Furthermore, the physiologic benefits of inhaled nitric oxide are short-lived, and there is no evidence of improvement in mortality (Griffiths 2005).

Epoprostenol is the most-studied alternative to inhaled nitric oxide to manage RV dysfunction and PH in the perioperative setting. Its effects on pulmonary hemodynamics are similar to those of inhaled nitric oxide, largely given data outside the cardiac surgical setting (i.e., acute respiratory distress syndrome, sepsis, severe heart failure, and PAH) (Griffiths 2005). Epoprostenol's half-life of 3–6 minutes has been extensively evaluated when given intravenously across a wide range of doses for various indications (5–120 ng/kg/minute) in both adult and pediatric patients (Fischer 2003; Eronen 1997). Limitations to intravenous epoprostenol use are systemic prostacyclin-related adverse effects such as hypotension, flushing, and jaw pain. Data analyses for inhaled epoprostenol (10–50 ng/kg/minute) are more limited but suggest that systemic toxicities such as hypotension and bleeding postsurgery are not clinically significant (Haraldsson 2000). Administering epoprostenol by this route can be a limitation because it requires a specialized delivery system (i.e., jet nebulizer) (Haraldsson 2000).

Finally, the PDE5 inhibitor class (i.e., sildenafil) has salutary effects on the pulmonary vasculature, as evidenced by its effectiveness in treating PAH (Galie 2005). Beyond the vasodilatory properties of PDE5 inhibitors, other pharmacologic effects include reduction in platelet activation, increase in RV contractility, and preconditioning of the myocardium (Simon 2013; Fung 2005). These pharmacologic effects have been hypothesized to confer cardioprotective (or "RV protective") benefits in the context of cardiac surgery, especially in the presence of CPB and PH (Fung 2005). One study showed

an augmentation of pulmonary vasodilation in the presence of inhaled nitric oxide for postoperative PH; however, clinical studies in the cardiac surgical setting are lacking (Atz 2002).

The use of mechanical RV support is beyond the scope of this section, but several options exist when pharmacologic therapy is unsuccessful. These options include balloon atrial septostomy, ECMO typically in a venoarterial arrangement, and more permanent devices such as an RV assist device or a total artificial heart (Simon 2013). Definitive therapy for end-stage RV failure is transplantation. Cardiac, lung, or a combined transplantation may be appropriate, depending on the underlying etiology of RV failure.

Heparin-Induced Thrombocytopenia in the Cardiac Surgery Patient

Screening and Diagnosis

Post-cardiac surgery patients are at higher risk of developing HIT, with a reported incidence as high as 3% compared with less than 1% in the medical population (Linkins 2012). However, the diagnosis of HIT in post-cardiac surgery patients can be complicated by thrombocytopenia inherently caused by CPB and unrelated to HIT because only a small fraction of post-cardiac surgery patients with thrombocytopenia actually have HIT. Various scoring tools and diagnostic approaches for HIT have been evaluated in different populations. The most widely studied prediction tool to assist with determining the probability of HIT is the 4T's score, which is easy to use and commonly accepted for assessing the clinical likelihood of HIT, but it can be limited by low positive predictive value and interobserver variability (Linkins 2012; Warkentin 2010). However, the high negative predictive value of the 4T's score makes it useful for quickly excluding patients from further costly and time-consuming diagnostic workup.

Another scoring tool, the HIT Expert Probability (HEP) score, although similar to the 4T's score, more specifically defines non-HIT causes of thrombocytopenia and addresses many cardiac surgery–specific causes of thrombocytopenia, including CPB and intra-arterial devices such as the intra-aortic balloon pump, LVAD, and ECMO. The HEP score is more cumbersome but reduces the interobserver variability seen with the 4T's score and may help assess the likelihood of HIT in the cardiac surgery population (Cuker 2010).

An additional predictive scoring tool, the Lillo-Le Louët model, is specifically intended for use in the post-CPB setting. As many as 15%–20% of patients undergoing cardiac surgery, with one report showing up to 50%, may develop antiplatelet factor 4 (anti-PF4) antibodies. Most of these cases will not progress to develop clinical HIT, but most will have some degree of thrombocytopenia associated with CPB. The Lillo-Le Louët model describes a clinical scoring tool to be used in patients with thrombocytopenia (Plt less than 150,000/mm^3 or a drop in platelets of more than 40% from baseline) after CPB. The tool uses two patterns of thrombocytopenia, together with the time since CPB and the duration of CPB, as independent variables to differentiate between thrombocytopenia associated with CPB and HIT (Lillo-Le Louët 2004). In pattern A, which is a stronger predictor of HIT, platelet count begins to recover after CPB but then begins to fall again more than 4 days after CPB; in pattern B, thrombocytopenia occurs immediately after CPB and persists for more than 4 days without recovery (Table 2-6).

Table 2-6. Lillo-Le Louët Screening Tool for Heparin-Induced Thrombocytopenia in Patients with Thrombocytopenia After CPB

Variable	Assessment	Points
Plt pattern	A – Biphasic pattern – initial fall immediately after CPB, followed by a recovery within 5 days and then a further fall > 4 days after CPB	2
	B – Persistent thrombocytopenia after CPB continuing beyond postoperative day 4	1
Time from CPB	≥ 5 days	2
	< 5 days	0
Duration of CPB	≤ 118 min	1
	> 118 min	0
Diagnostic Probability of HIT		Total
High probability		≥ 2
Low probability		< 2

CPB = cardiopulmonary bypass. Plt = platelet

Information from: Lillo-Le Louët A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. J Thromb Haemost 2004;2:1882-8.

Patient Care Scenario

A 59-year-old woman is admitted to the ICU after CABG × 3 with bioprosthetic aortic valve replacement on CPB for 129 minutes. Her initial postoperative course was complicated by hypotension requiring vasopressors, necessitating a prolonged ICU stay. She is now postoperative day 6 and develops thrombocytopenia with a platelet trend as follows:

Postoperative Day	Platelet Count (×10³/mm³)
Preoperative	305
0 (surgery)	157
1	150
2	162
3	177
4	204
5	140
6	95

She received heparin during CPB and has received subcutaneous heparin for deep venous thrombosis prophylaxis since surgery, but she has had no recent hospital admissions or previous exposure to heparin. The clinician must decide the next appropriate step for evaluating thrombocytopenia.

ANSWER

First, evaluate the patient's likelihood of having HIT. Consider the inherent drop in Plt associated with surgery and CPB, which explains her initial drop in Plt from her preoperative baseline to immediately postoperatively. This drop in Plt is common and not associated with HIT. The patient's Plt then recovers to her new postoperative baseline of 204,000/mm³ before dropping to 95,000/mm³ in 2 days. At this point, various causes of thrombocytopenia must be considered, including HIT. Any of the many different scoring tools can be considered to determine a pretest probability for HIT. According to the 4T's score: the patient has a Plt drop of more than 50% with a NADIR greater than 20,000/mm³ and no surgery within the previous 3 days (2 points), a drop in Plt beginning 5 days after exposure to heparin with no known previous exposure (2 points), no known new thrombosis (0 points), and no known other causes (2 points), according to the information provided. The patient's 4T's score is 6, indicating a high likelihood of HIT. The clinician may also consider the Lillo-Le Louët screening score, an alternative prescreening tool directed specifically at the post-cardiac surgery population. Given the Lillo-Le Louët score, the patient has a biphasic Plt pattern (2 points), 5 days from CPB (2 points), with a prolonged CPB duration (0 points), again indicating a high pretest probability for HIT. It should be recommended to send an anti-PF4 laboratory test to evaluate for HIT. In addition, heparin should be withheld, and initiation of direct-thrombin inhibitor for treatment of HIT should be strongly considered.

1. Lillo-Le Louët A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. J Thromb Haemost 2004;2:1882-8.
2. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(suppl):e495S-e530S.

In general, the 4T's score remains the most commonly used tool for assessing the clinical probability of HIT, but the HEP score and Lillo-Le Louët model may be useful in the post-cardiac surgery setting.

Anticoagulation Management for Patients with HIT Requiring Cardiac Surgery

Heparin is commonly used during cardiac surgery to avoid thrombosis associated with blood exposure to the CPB system and tissue factor exposure in the operative field. Compared with other anticoagulant options, heparin is preferred because of its short half-life, rapid onset, rapid neutralization with protamine sulfate, low cost, and ease of monitoring. However, alternative strategies must be considered for patients with HIT requiring cardiac surgery. The two anticoagulation approaches for such patients who require urgent cardiac surgery are (1) the use of a non-heparin anticoagulant (e.g., a direct thrombin inhibitor); or (2) the combination of heparin with a platelet inhibitor (e.g., a glycoprotein IIb/IIIa inhibitor) to attenuate the platelet activation response associated with heparin. In nonemergencies, cardiac surgery may be delayed until the transient HIT antibodies are no longer detectable (usually about 50–80 days), and CPB can be performed with standard heparin with an alternative postoperative anticoagulation approach (Linkins 2012).

Although bivalirudin is the most studied and well-accepted agent for anticoagulation for CPB in patients with HIT requiring cardiac surgery, its evidence remains limited to small prospective cohorts lacking internal controls and retrospective cases. The CHOOSE-ON trial was an open-label, multicenter trial assessing the safety and efficacy of bivalirudin for anticoagulation in 49 patients with HIT undergoing CPB for noncomplicated CABG or valve surgery. The anticoagulation protocol involved bivalirudin given as a 1-mg/kg intravenous bolus, followed by a continuous infusion of 2.5 mg/kg/hour until 15 minutes before the planned end

of CPB, in addition to a 50-mg priming bolus added to the CPB circuit, with a goal ACT greater than 2.5 times baseline. In-hospital acute procedural success was achieved in 94% of patients, and the authors concluded that bivalirudin was safe and effective (Koster 2007). In the CHOOSE-OFF trial, the same group described a 92% procedural success with an acceptable incidence of bleeding or transfusions in 51 patients with HIT receiving bivalirudin undergoing off-pump CABG, using a slightly less aggressive bivalirudin dosing regimen (0.75-mg/kg bolus; then 1.75 mg/kg/hour with goal ACT greater than 300 seconds) (Dyke 2007). Evidence shows that bivalirudin is a viable alternative to heparin, and guidelines recommend its use over other non-heparin anticoagulants in patients with HIT requiring urgent cardiac surgery (Linkins 2012). Further research is needed to identify optimal dosing and monitoring values.

Because of the pharmacokinetics of bivalirudin, additional consideration should be given to patients with HIT undergoing more complicated cardiac surgical procedures requiring deep hypothermic circulatory arrest. Bivalirudin has a short elimination half-life of around 25 minutes, with elimination primarily through enzymatic degradation by plasma proteases and thrombin, together with about 20% renal clearance. During CPB, regions of blood stasis within the circuit or patient may result in local decreases in bivalirudin concentrations from enzymatic degradation, which can further be exacerbated by lack of circulation during deep hypothermic circulatory arrest. This impact of enzymatic degradation on bivalirudin necessitates surgical techniques to avoid blood stagnation that can result in decreased bivalirudin efficacy and ultimately thrombosis. If cell-saving devices are used to re-transfuse blood, citrate-based products (e.g., anticoagulant citrate phosphate dextrose, anticoagulant citrate-dextrose solution A) should be used in place of heparin to anticoagulate salvaged blood. Inactivation of bivalirudin in the stagnant blood of a cell-saving device prohibits its use in such capacities.

Further complicating the use of bivalirudin in deep hypothermic circulatory arrest is the negative impact of hypothermia on enzymatic activity. Hypothermia can significantly reduce bivalirudin proteolysis, resulting in increased anticoagulant effects (Leissner 2007; Greinacher 2004). Because of a lack of evidence, no specific recommendations exist for managing these situations, but anticoagulant effects should be monitored with ACT or ecarin clotting time. Despite these concerns, successful use of bivalirudin has been described in patients with HIT requiring deep hypothermic circulatory arrest (Koster 2013; Leissner 2007).

Finally, an alternative approach to bivalirudin in patients with HIT requiring cardiac surgery involves the use of heparin in combination with a glycoprotein IIb/IIIa antagonist for inhibition of platelet activation. One study reported a series of 10 patients with HIT and renal impairment undergoing CPB who were anticoagulated with heparin after a bolus and continuous infusion of tirofiban. No increased postoperative bleeding or thromboembolic complications were reported (Koster 2001a). Additional retrospective data of the same approach in 47 patients with HIT undergoing cardiovascular surgery showed similar success in safety and efficacy (Koster 2001b).

Ultimately, consensus guidelines recommend the use of bivalirudin for patients who require urgent cardiac surgery with acute HIT or subacute HIT or for those with a history of HIT in whom heparin antibodies are still present. In nonurgent cases, cardiac surgery should be delayed until HIT has resolved and HIT antibody assays are negative, and heparin should be used for anticoagulation during surgery. In such cases, heparin exposure should be limited to the time of surgery, and an alternative anticoagulation plan should be used in the postoperative period (Linkins 2012).

Practice Points

When determining the optimal pharmacotherapy for the perioperative treatment of cardiac and vascular surgery patients, practitioners should consider the following:

- **Atrial fibrillation is the most common postoperative complication of cardiothoracic surgery, occurring in 25%–50% of cases. β-Blockers are recommended first line for prevention and treatment of POAF.**
- **The incidence of HIT in cardiac surgery is higher than in many other patient populations. Screening tools such as the HEP score and the Lillo-Le Louët model are useful in assessing the likelihood for HIT and the need for further diagnostic testing and treatment. In patients who develop HIT, treatment involves use of direct thrombin inhibitors and is consistent with treatment in other populations. Various strategies exist for intraoperative anticoagulation for patients with HIT requiring CPB, the most common of which includes bivalirudin.**
- **Treatment of coagulopathy associated with cardiac surgery is primarily supportive. In life-threatening hemorrhage associated with coagulopathy after cardiac surgery, PCCs and rFVIIa have each been used with varying success and potential safety concerns.**
- **In patients requiring MCS, therapy modifications to address anticoagulation, atypical hemodynamic changes, and pharmacokinetic factors are essential considerations.**
- **Postoperative vascular surgery patients are at risk of various complications after surgery. Preventing cardiac events (e.g., MI) and neurological events (e.g., spinal cord ischemia) after aortic aneurysm repair is an important focus of pharmacotherapy.**

CONCLUSION

Care of the cardiovascular surgery patient is broad and often specific to the type of procedure. Thrombosis and hemostasis, together with appropriate anticoagulation strategies, are important considerations in such patients to treat and prevent complications. Hemodynamic management and cardiac rhythm control are also central focuses in the perioperative treatment of cardiovascular surgery patients to optimize

outcomes. Although strong guidelines and recommendations exist for certain areas such as the care of patients post-CABG and cardiac surgery patients with HIT, other emerging areas such as managing MCS and treating coagulopathy are less well studied and require further evidence to fully elucidate best practice approaches.

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Self-Assessment Questions

Questions 21 and 22 pertain to the following case.

J.C., a 72-year-old man with a history of hypertension, atrial fibrillation (AF), transient ischemic attack, and coronary artery disease (CAD) with previous non–ST-segment elevation myocardial infarction (non-STEMI), is admitted for elective coronary artery bypass grafting (CABG) surgery. His relevant home drugs include aspirin 81 mg daily, metoprolol tartrate 50 mg twice daily, and nifedipine extended release 90 mg daily. J.C. has no known drug allergies. His preoperative blood pressure is 126/66 mm Hg, heart rate is 82 beats/minute, and arterial oxygen saturation (Sao_2) is 98%. J.C.'s laboratory test results are unremarkable.

21. Assuming that J.C.'s home drugs are continued during his admission, which one of the following is best to add daily to his preoperative regimen?

    A. Clopidogrel 75 mg
    B. Atorvastatin 40 mg
    C. Lisinopril 5 mg
    D. Multivitamin 1 tablet

22. In the perioperative setting, which one of the following goals related to blood glucose management would be best to recommend for J.C.?

    A. Less than 200 mg/dL to minimize severe hypoglycemia
    B. 150–200 mg/dL to provide permissive hyperglycemia
    C. 180 mg/dL or less to decrease the risk of sternal wound infections
    D. 70–110 mg/dL to reduce the risk of perioperative myocardial infarction

Questions 23 and 24 pertain to the following case.

S.H., a 62-year-old man with a history of class IV heart failure, is admitted to the ICU after a HeartMate II left ventricular assist device (LVAD) implantation. After 12 hours in the ICU, S.H.'s vital signs are as follows: mean arterial pressure (MAP) 61 mm Hg, heart rate 97 beats/minute, cardiac index (CI) 1.9 L/minute/m^2, Svo_2 47%, and central venous pressure (CVP) 9 mm Hg, with decreased urine output. In the operating room, he has minimal LV ejection on echocardiography. Postoperatively, his Hgb is 10.5 g/dL, Hct is 31.3%, Plt is 191,000/mm^3, and chest tube output is about 10 mL/hour over the past 6 hours.

23. Which one of the following is best to initiate to improve S.H.'s hemodynamics?

    A. Epinephrine 1–5 mcg/minute
    B. Milrinone 0.25 mcg/kg/minute
    C. Dopamine 5 mcg/kg/minute
    D. Inhaled nitric oxide

24. Which one of the following is best to recommend as an antithrombotic regimen for S.H.'s LVAD?

    A. Initiate full-dose intravenous heparin with loading dose for a goal aPTT of 60–80 seconds.
    B. Initiate bivalirudin for a goal aPTT of 1.5–2.0 times baseline.
    C. Initiate aspirin today, and consider initiating intravenous heparin tomorrow
    D. Initiate warfarin 5 mg today.

25. A 20-year-old woman presents with cystic fibrosis requiring VV-ECMO for refractory hypoxemic respiratory failure; she is awaiting lung transplantation. The patient is currently sedated on fentanyl 250 mcg/hour and midazolam 5 mg/hour. She develops a temperature of 38.7°C while receiving ECMO, with WBC increased to 18 × 10^3 cells/mm^3, and will be initiated on empiric vancomycin and piperacillin/tazobactam for possible ventilator-associated pneumonia. Notable laboratory values are as follows: ALT 37 IU/L, AST 46 IU/L, total bilirubin 0.9 mg/dL, SCr 0.7 mg/dL, and BUN 16 mg/dL. Which one of the following would be best to recommend for her drug therapy with respect to the effects of ECMO on her medications?

    A. ECMO will decrease the Vd of vancomycin, resulting in the need for a more conservative loading dose to avoid accumulation.
    B. Fentanyl may be significantly sequestered by the ECMO circuit, resulting in increased dosing requirements or the need to change to a less lipophilic analgesic agent such as hydromorphone.
    C. Piperacillin/tazobactam should be changed to meropenem for empiric coverage because meropenem is less affected by ECMO.
    D. Vancomycin will require more frequent dosing because of sequestration by the ECMO circuit.

26. Which one of the following hemodynamic parameters would most likely be present in a patient developing right ventricular (RV) dysfunction after LVAD implantation?

    A. Increased CVP with RV dilation on echocardiography
    B. Decreased CVP with RV compression on echocardiography
    C. Decreased CVP with underfilled RV on echocardiography
    D. Increased CVP with rightward septal shift on echocardiography

27. A 71-year-old woman who has had thoracic endovascular aortic repair is postoperatively admitted to the vascular ICU. At 12 hours postoperatively, she develops decreasing sensation and decreased motor strength in her bilateral lower extremities. The pressure from her

CSF drain, placed intraoperatively, is optimized by the medical team. Pertinent vital signs and laboratory test results are as follows: heart rate 87 beats/minute, MAP 64 mm Hg, SCr 1.1 mg/dL, Hgb 9.3 g/dL, Hct 29.0%, and Plt 211,000/mm^3. Which one of the following is best to recommend for this patient?

A. 1 unit of packed red blood cells
B. Vasopressin 0.03 units/minute with goal MAP 70-80 mm Hg
C. Norepinephrine 2 mcg/minute titrated to goal MAP of 80–90 mm Hg
D. Milrinone 0.25 mcg/kg/minute titrated to CI greater than 2.2 L/minute

28. A 65-year-old man presents with cold extremity, nonpalpable pedal pulses occasionally heard on Doppler. The patient has 8/10 pain in his left lower extremities with moderate sensory deficit starting yesterday morning. He has a history of CAD (after CABG × 2 in 2003 and CABG × 3 with aortic valve replacement in 2009) with ongoing unstable angina, hypertension, type 2 diabetes, and hypothyroidism. It is determined that he will require reperfusion therapy for acute limb ischemia. Which one of the following is best to recommend for this patient?

A. Catheter-directed thrombolysis (CDT) with streptokinase
B. CDT with alteplase
C. Heparin only with a planned bridge to Coumadin
D. An open surgical revascularization approach

29. A 67-year-old man with a history of AF and heart failure presents with aortic dissection requiring urgent surgical intervention. At home, he was receiving metoprolol succinate 100 mg daily, aspirin 81 mg daily, rivaroxaban 20 mg daily, lisinopril 10 mg daily, furosemide 20 mg twice daily, and atorvastatin 20 mg daily. The surgeon requests an agent to reverse the anticoagulant effects of rivaroxaban to minimize bleeding. Which one of the following is best to recommend to minimize bleeding in this patient?

A. Initiate dialysis to remove rivaroxaban before surgery.
B. Give four-factor prothrombin complex concentrate (4F-PCC) 50 units/kg.
C. Give 1 unit of fresh frozen plasma.
D. Give idarucizumab 5 g.

Questions 30–32 pertain to the following case.

J.T. is a 69-year-old woman (weight 95 kg) with a medical history of hypertension, obesity (BMI 40 kg/m^2), dyslipidemia, type 2 diabetes, and CAD. She is scheduled to undergo CABG with mitral valve repair. Her current drugs include hydrochlorothiazide 25 mg daily, amlodipine 10 mg daily, aspirin 81 mg daily, atorvastatin 20 mg daily, and lisinopril 10 mg daily.

30. Which one of the following is best to recommend for prophylaxis of postoperative atrial fibrillation (POAF) for J.T.?

A. Diltiazem 60 mg orally every 6 hours, titrated to a resting heart rate of 80 beats/minute
B. Digoxin 0.25 mg orally daily
C. Amiodarone 10 mg/kg orally daily in divided doses, given 6 days presurgery through 6 days postsurgery
D. Amiodarone 400 mg orally daily for 14 days, starting immediately before surgery

31. J.T. underwent successful CABG and mitral valve repair, but her clinical course was complicated on postoperative day 2 by new-onset AF. Her blood pressure at that time was 112/54 mm Hg with a heart rate of 145 beats/minute. Her laboratory values were all within normal limits. Which one of the following is best to recommend for initial treatment of J.T.'s POAF?

A. Amiodarone 1.2 g intravenously over 24 hours
B. Magnesium sulfate 2 g intravenously
C. Colchicine 1.2 mg orally × 1; then 0.6 mg orally twice daily
D. Metoprolol 5 mg intravenous bolus over 2 minutes

32. On postoperative day 4 (48 hours after the onset of POAF), J.T. remains in AF with a heart rate of 120 beats/minute despite intermittent boluses of β-blockers. Her blood pressure remains stable at 105/50 mm Hg; however, she has intermittent shortness of breath and palpitations. A transthoracic echocardiogram reveals no evidence of thrombus. The patient currently receives heparin intravenously according to an institutional nomogram. Which one of the following is best to recommend for J.T.?

A. Verapamil 2.5 mg intravenously over 2 minutes
B. Ibutilide 1 mg intravenously over 10 minutes
C. Metoprolol 5 mg intravenously every 5 minutes × 3
D. Amiodarone 200 mg orally once daily

33. A 54-year-old man with a history of type 2 diabetes, smoking, and hypertriglyceridemia is admitted to the hospital for management of an anterior STEMI complicated by left ventricular dysfunction (ejection fraction of 25% with severe anteroapical hypokinesis by echocardiogram). He is found to have triple-vessel disease during left heart catheterization. Right heart catheterization reveals a CI of 1.6 L/minute/m^2 (reference 2.5–4 L/minute/m^2), pulmonary capillary wedge pressure of 24 mm Hg (reference 6–12 mm Hg), CVP of 5 mm Hg (reference 2–6 mm Hg), and systemic vascular resistance of 1300 dynes/second/cm^5 (range 800–1200 dynes/second/cm^5). His vital signs include blood pressure 90/60 mm Hg, heart rate 110 beats/minute, and Sao_2 92%. He is being transferred to the cardiothoracic ICU with plans for urgent CABG surgery. Chest radiography is remarkable for bilateral pulmonary edema. The patient is ordered a dose of furosemide 40 mg intravenously twice daily. His other

notable inpatient drugs include aspirin, atorvastatin, and heparin intravenously. His SCr is 1.9 mg/dL (baseline 1.1 mg/dL). Which one of the following intravenous vasoactive medications is best to recommend for this patient?

A. Dopamine 5 mcg/kg/minute infusion titrated to MAP greater than 60 mm Hg
B. Milrinone 0.5 mcg/kg/minute infusion titrated to systolic blood pressure greater than 90 mm Hg
C. Norepinephrine 0.05 mcg/kg/minute infusion titrated to MAP greater than 60 mm Hg
D. Dobutamine 5 mcg/kg/minute infusion titrated to CI greater than 2.2 L/minute/m^2

34. Which one of the following considerations is most relevant when deciding which inotrope to initiate for a patient in cardiogenic shock?

A. History of hypertension
B. Hepatic function
C. Initial systolic blood pressure
D. Recent use of a CCB

35. A 65-year-old woman is admitted to the cardiothoracic ICU postoperatively after a second-time CABG × 3 with aortic valve replacement and mitral valve repair. In the operating room, she received 9 units of packed red blood cells, 7 units of fresh frozen plasma, 5 six-packs of platelets, and 3 ten-packs of cryoprecipitate for profound coagulopathy and continued further transfusions in the ICU. Her chest was packed and remains open on arrival to the ICU. Chest tube output since ICU arrival 3 hours earlier has averaged 250 mL/hour. The surgeon notes no known surgical source of bleeding, and she received 50 mg of protamine before transfer from the operating room. Pertinent laboratory values are as follows: Hgb 6.8 g/dL, Hct 20.2%, Plt 57,000/mm^3, INR 1.6, aPTT 41 seconds, and fibrinogen 210 mg/dL. Which one of the following recommendations and justification is best for treating this patient's coagulopathy after cardiac surgery?

A. 4F-PCC should be considered in this setting because of the high likelihood of disseminated intravascular coagulation.
B. rFVIIa is indicated for this patient because it is associated with improved outcomes in cardiac surgery patients.
C. 3F-PCC has been associated with decreased postoperative blood loss when used as first-line treatment for coagulopathy after cardiac surgery and may be considered to reduce further blood loss.
D. rFVIIa should be considered because it has not been associated with an increased risk of thromboembolic events when used to treat coagulopathy associated with cardiopulmonary bypass (CPB).

Questions 36–38 pertain to the following case.

C.J. is a 74-year-old man (weight 120 kg) with a medical history of hypertension, obesity (BMI 38 kg/m^2), obstructive sleep apnea, and CAD with recent CABG. His postoperative course is complicated by the development of moderate to severe RV dysfunction confirmed by echocardiography. Hemodynamic measurements reveal the following: CVP 12 mm Hg (reference 2–6 mm Hg), pulmonary capillary wedge pressure 12 mm Hg (reference 6–12 mm Hg), CI 1.9 L/minute/m^2 (reference 2.5–4 L/minute/m^2), pulmonary artery pressure (PAP) 48/24 mm Hg (reference 15–30/8–15 mm Hg) with a mean PAP of 32 mm Hg (reference 9–18 mm Hg), and pulmonary vascular resistance (PVR) 420 dynes/second/cm^5 (range less than 250 dynes/second/cm^5). His current vital signs are blood pressure 102/55 mm Hg, heart rate 92 beats/minute, and Sao_2 94%. C.J. has shortness of breath, and his clinical examination is remarkable for jugular venous distention, hepatomegaly, and 3+ peripheral edema bilaterally. His extremities are also cool to the touch. His SCr is 1.7 mg/dL (baseline 1.3 mg/dL).

36. Which one of the following is best to recommend as initial treatment of C.J.'s RV failure?

A. Norepinephrine 0.05 mcg/kg/minute intravenous infusion, titrated to systolic blood pressure greater than 90 mm Hg
B. Bumetanide 1-mg intravenous bolus × 1, with reassessment of volume status
C. Furosemide 40 mg orally once daily
D. Sildenafil 80 mg orally three times daily

37. Which one of the following inotropes would be best to recommend as intravenous infusion for C.J.?

A. Dobutamine 2.5 mcg/kg/minute
B. Epinephrine 0.05 mcg/kg/minute
C. Milrinone 0.25 mcg/kg/minute
D. Phenylephrine 0.1 mcg/kg/minute

38. Which one of the following adjunctive recommendations would best manage C.J.'s pulmonary hypertension?

A. Inhaled nitric oxide 10 ppm
B. Inhaled epoprostenol 200 ng/kg/minute
C. Intravenous sildenafil 20 mg three times daily
D. Inhaled milrinone according to protocol

39. A 64-year-old woman with CAD (10 months after bare metal stents × 2), diabetes, hypertension, stage 2 chronic kidney disease, and a history of heparin-induced thrombocytopenia (HIT) (deep venous thrombosis [DVT] 10 months earlier) presents for a planned three-vessel on-pump CABG with aortic valve repair. Pertinent laboratory values from this morning include Plt 195,000/mm^3, Hgb 9.2 g/dL, Hct 27.5%, and anti-PF4 optical density

0.087 (normal range: less than 0.400). Which one of the following is best to recommend for this patient's anticoagulation during CPB for her cardiac surgery?

A. Tirofiban 10-mcg/kg bolus, followed by a continuous infusion of 0.15 mcg/kg/minute in combination with heparin 300 units/kg adjusted to reach goal ACT
B. Bivalirudin 50-mg pump priming dose with 1 mg/kg intravenous bolus, followed by a continuous infusion of 2.5 mg/kg/hour adjusted to goal ACT
C. Bivalirudin 0.75 mg/kg bolus; then 1.75 mg/kg/hour adjusted to reach ACT
D. Heparin 250–300 units/kg adjusted to reach ACT

40. A 55-year-old woman who is admitted to the ICU after aortic valve replacement and mitral valve repair develops thrombocytopenia. She has no recent admissions or no prior surgery. Her surgery was uncomplicated, and she received heparin for CPB. Her preoperative Plt was 239,000/mm^3, which dropped to 112,000/mm^3 on postoperative day 1 and is now 103,000/mm^3 on postoperative day 2. She has no signs of thrombosis or bleeding and is initiated on subcutaneous heparin on postoperative day 1 for DVT prophylaxis. The team is concerned about HIT because of her platelet count. Which one of the following is best to recommend for this patient?

A. Probability of HIT is high; send an anti-PF4, and change from heparin to fondaparinux.
B. Probability of HIT is high; send an anti-PF4, but continue subcutaneous heparin pending the results.
C. Probability of HIT is low; send anti-PF4 laboratory test to rule out, but continue subcutaneous heparin.
D. Probability of HIT is low; continue to monitor Plt for persistent or worsening thrombocytopenia.

Learner Chapter Evaluation: Perioperative Management: Cardiac and Vascular Surgery.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

18. The content of the chapter met my educational needs.
19. The content of the chapter satisfied my expectations.
20. The author presented the chapter content effectively.
21. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
22. The content of the chapter was objective and balanced.
23. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
24. The content of the chapter was useful to me.
25. The teaching and learning methods used in the chapter were effective.
26. The active learning methods used in the chapter were effective.
27. The learning assessment activities used in the chapter were effective.
28. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

29. Design evidence-based therapeutic regimens to improve outcomes in post-cardiac surgery patients.
30. Apply strategies for supportive care in patients requiring mechanical circulatory support.
31. Design therapeutic regimens to treat and prevent complications in vascular surgery patients.
32. Evaluate for potential complications after cardiac surgery, and apply evidence-based strategies to prevent and/or treat them.
33. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
34. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Perioperative Management: Transplantation and Neurosurgery

By Heather Personett, Pharm.D., BCPS, BCCCP; and Hira Shafeeq, Pharm.D., BCPS

Reviewed by Christine A. Lesch, Pharm.D., BCPS; Shawn E. Fellows, Pharm.D., BCPS; and Russell Dixon, Pharm.D., BCCCP

LEARNING OBJECTIVES

1. Apply preventive therapies and design a response to severe adverse effects of immunosuppression in the peri- and post-transplant period.
2. Develop an antimicrobial treatment plan for a transplant recipient whose donor had a confirmed infection.
3. Justify prevention and treatment strategies for post-transplant allograft thrombosis.
4. Design medication adjustments in the setting of significant immunosuppressant drug interactions.
5. Construct therapies to prevent complications such as perioperative epilepsy and postoperative infection in neurosurgical patients.
6. Compose a plan for pre-operative coagulopathy reversal in neurosurgical patients.
7. Assess analgesia and sedation therapies in neurologically injured patients.
8. Design an evidence-based treatment protocol for management of neurologic emergencies.

ABBREVIATIONS IN THIS CHAPTER

CNI	Calcineurin inhibitor
CPP	Cerebral perfusion pressure
HCV	Hepatitis C virus
HIT	Heparin-induced thrombocytopenia
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
MAP	Mean arterial pressure
SAH	Subarachnoid hemorrhage
SDH	Subdural hemorrhage

Table of other common abbreviations.

CONSIDERATIONS IN SOLID ORGAN TRANSPLANTATION

Critical Care Complications of Immunosuppression

The use of immunosuppressive agents is essential to the success of solid organ transplantation. Unfortunately, these drugs come with an extensive list of potential adverse effects, several of which may require escalation of care. Several such complications relevant to the ICU pharmacist are discussed here.

Anti-thymocyte Globulin Infusion Reactions

Induction agents are used to create profound and enduring lymphocyte suppression in the immediate peri-transplant period, as well as to treat organ rejection. One agent commonly used for these purposes is anti-thymocyte globulin (ATG), a polyclonal antibody created by purifying IgG produced in response to inoculation of rabbits or horses with human lymphocytes. These antibodies are directed against a host of cell-surface molecules, targeting T and B cells, natural killer cells, and macrophages. After introduction of these xenogenic proteins to the immune system, T cells experience partial activation, which can lead to massive cytokine release with sequelae serious enough to require intensive care. This risk is highest

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic knowledge of drug classes used for immunosuppression, including mechanism of action and major clinical effects
- General understanding of the pathophysiology of HIV and approach for treatment
- General understanding of the pathophysiology of HCV and approach for treatment
- General pathophysiology of epilepsy
- General understanding of management of hemorrhagic strokes (SAH, ICH and SDH)
- General understanding of pain and sedation principles for mechanically ventilated patients

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Institute of Health. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
- The Liverpool HIV Pharmacology Group. www.hiv-druginteractions.org.
- American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitic C.
- University of Liverpool. www.hep-druginteractions.org.
- Neurocritical Care Society and Society of Critical Care Medicine. Guideline for Reversal of Antihtombotics in Intracranial Hemmorage.
- Neurocritical Care Society Guidelines for Management of Subarachnoid Hemorrhage. Critical Care Management of Patients following aSAH.
- American Heart Association/American Stroke Association Guidelines for Intracerebral Hemorrhage. Guidelines for Management of Spontaneous ICH.
- Rowe, A. S., H. Goodwin, G. M. Brophy, et al. Seizure prophylaxis in neurocritical care: a review of evidence-based support. Pharmacotherapy 2014;34:396-409.
- The American College of Surgeons Trauma Quality Improvement Program-Best Practices in the Management of Traumatic Brain Injury.
- Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement

during the initial dose (up to 80% of patients experience varying degrees of symptoms) but persists with subsequent doses (Guttmann 1997).

Significant reactions to ATG include anaphylaxis, serum sickness, acute respiratory distress, and acute kidney injury. In the case of anaphylaxis, symptoms of noticeable swelling, upper airway edema with subsequently poor ventilation, and hemodynamic collapse appear within minutes of the start of infusion. Response to epinephrine and steroid therapy has been reported; however, repeated challenge with the agent should not be attempted (Sebeo 2012). Signs of serum sickness may include hyperthermia, hypotension requiring vasopressors, and significant tachycardia or bradycardia. Respiratory distress manifesting as tachypnea and wheezing may respond to bronchodilators in some cases, or in the event of refractory or severe symptoms, prolong the need for mechanical ventilation after transplantation or prompt intubation of a patient receiving ATG. Steroids, if not already given before the ATG infusion, may help blunt the systemic inflammatory response. Such cardiopulmonary reactions may occur during infusion or as a delayed reaction seen several hours following completion of administration (Busani 2006; Loushin 2001). In an attempt to mitigate symptoms, initial infusions are typically given over 6 hours and preceded by steroids, diphenhydramine, and acetaminophen. In the absence of symptoms, subsequent infusions may take place over 4 hours, though pre-treatment is still recommended.

Posterior Reversible Leukoencephalopathy Syndrome

Neurotoxicity is one of the most commonly encountered adverse effects of calcineurin inhibitors (CNIs); the most severe manifestation is posterior reversible leukoencephalopathy syndrome (PRES). Brain tissue hypoperfusion results from cerebral edema, either from inflammatory-mediated vascular endothelial damage or disruption of autoregulation as a consequence of severe systemic hypertension (Bartynski 2008). Evidence of this is best seen on MRI (the gold standard for PRES diagnosis) but may also be visualized by CT scan. Symptoms commonly associated with PRES include elevated blood pressure; seizure activity (usually preceded by vision changes or headache); and encephalopathy, which can range from mild disruption of consciousness or lethargy to severe agitation or coma. Although hypertension is often considered a hallmark of PRES, it is not present in all cases: some epidemiologic data describe a mean arterial pressure (MAP) exceeding 115–130 mm Hg, whereas other data suggest that about 50% of patients present with normal or only slightly elevated blood pressure (Bartynski 2008; Lee 2008). The risk of PRES is highest within the first 30 days of initiation of CNI therapy, although occurrences have been described as much as 10 months later (Heidenhain 2009). In some instances, PRES manifests in the setting of rapidly increasing or elevated concentrations (typically >12–15 ng/mL for tacrolimus);

however it can be seen at usual therapeutic concentrations as well. This may indicate that blood concentrations do not accurately reflect those present in the brain.

If a CNI is determined to be the cause of or a contributing factor for the development of PRES, syndromal reversal ultimately depends on adjustment of therapy in the form of dose reduction or discontinuation. Providers typically withdraw CNIs upon initial recognition of PRES. However, for patients in whom this therapy is overwhelmingly favorable (e.g., patients at high risk of rejection or with an additional compelling indication for a CNI) , several cases detail successful and sustained resolution of symptoms with a reduction in the target blood concentration or by switching to a different agent within the same class (Heidenhain 2009; Horbinski 2009; Thyagarajan 1997).

Symptomatic management should include cessation of seizures (preferably with a benzodiazepine), electrolyte optimization, and hemodynamic stabilization to the patient's premorbid baseline. Secondary prevention with antiepileptic therapy is not recommended. Given the suspected role of cerebral hypoperfusion in the pathophysiology of PRES, rapid over-correction and persistent hypotension should be avoided. With severe hypertension, similar to the treatment of hypertensive emergency, it is reasonable to lower MAP by 25% within the first hour of presentation, with a gradual reduction to the patient's baseline blood pressure over the next 24–48 hours (Strandgaard 1984) Improvement of symptoms such as altered mental status or visual changes is typically seen within several days of treatment, though notably it may lag behind normalization of CNI blood concentrations.

Donor-Derived Infection

Definition and Epidemiology

Criteria for organ donation are expanding as the need for transplantation continues to exceed the supply of available organs. As a result, more marginal specimens and high-risk donors are considered candidates, increasing the risk of infection in recipients. Infection transmission is possible when a donor has an active infection from any source including blood, urine, or the CNS. Some infections may be anticipated (e.g., cytomegalovirus, hepatitis B) and routinely managed proactively with prophylaxis or pre-emptive therapy. Others are unexpected and carry a high risk of morbidity and mortality. Though previously reported in less than 1% of cases, current data suggest these rates are increasing, with an attributable mortality of up to 30% (Green 2015; Ison 2013). Additionally, a lack of infection recognition and underreporting may mask the true incidence of the problem.

Evidence suggests bacterial pathogens are the most common source of donor-derived infection. Published case reports identify involvement of both gram-positive and gram-negative organisms, including several multi-drug–resistant strains of *Pseudomonas* spp. and methicillin-resistant *Staphylococcus aureus*. Viral and fungal donor-derived infections have also been reported. Pneumonia, endocarditis, and septic arthritis are among the infectious complications detailed in the literature (Green 2015; Miceli 2015; Watkins 2012; Wendt 2014). Infection with gram-negative bacilli appears to be associated with the greatest risk of transmission and poorer patient outcomes (Ison 2013).

Risk Assessment

Recognition of individuals at high risk of infection transmission remains a crucial element of caring for potential organ donors. These include people with high-risk sexual contacts; those having received treatment for syphilis, gonorrhea, chlamydia, or genital ulcers within 12 months; prison inmates; intravenous drug users; and those having undergone dialysis within 12 months (Ison 2013). A heightened awareness of risk for donor-derived infection should result in closer surveillance for clinical, serologic, and microbiology signs of infection. Upon suspicion or identification of an active infection in an organ donor, appropriate antimicrobial therapy should be initiated and, in the case of confirmed infection, organism speciation and susceptibilities should be elucidated and reported.

Role of Antimicrobial Therapy

Guidelines address the treatment of infected organ donors and recipients of these allografts. If possible, individuals with bacterial meningitis or bacteremia at the time of donation should be treated with targeted antimicrobial therapy for 24–48 hours before organ procurement. Recipients of an organ from a donor with any type of infection are recommended to receive antimicrobials to which the isolated organism is susceptible for 7–14 days after transplantation (Ison 2013). Expanding the spectrum of activity of perioperative prophylaxis to include coverage of organisms known to have been isolated in a donor has failed to prevent transmission in several cases. This reinforces the need for a full treatment course with targeted antimicrobial therapy beyond routine perioperative prophylaxis. Additionally, several cases report the occurrence of possible or probable donor-derived infections weeks outside the immediate peri-transplant period, after presumed eradication of active infection in the recipient (Miceli 2015; Wendt 2014). As such, this must be considered when evaluating transplant patients presenting with acute decompensation in clinical status.

Coagulation and Thrombotic Complications

Critical care practitioners often encounter unique coagulopathy issues when caring for solid organ transplant patients; several of these are described here.

Pancreatic allograft thrombosis is a leading cause of early graft loss. Because of this risk, several early prevention strategies have been investigated. Unfractionated heparin started within 24 hours of transplant has been shown to reduce the risk of thrombosis in the immediate postoperative

period. Rates range from 100–500 units/hour and most commonly are not titrated based on aPTT changes (Farney 2012; Scheffert 2014). One study describes titration of unfractionated heparin to maintain a goal aPTT of twice the patient's baseline values. This strategy was then compared with prophylactic doses of low molecular weight heparin and shown to be equally effective without significant differences in bleeding (Schenker 2009). Postoperative aspirin is also recommended, because patients receiving a pancreas transplant for diabetes mellitus also have an indication for lifelong cardioprotective aspirin. Some expert opinion endorses 81 mg daily; however, 325 mg daily can be considered in patients with other comorbid diagnoses conferring a high risk for thrombosis (Farney 2012). Warfarin is generally avoided in the absence of a separate compelling indication, and there are no data describing the use of direct oral anticoagulants in this population. To mitigate allograft thrombosis risk, it is important to consider which intervention may be appropriate early in the postoperative period once the patient is safe to begin anticoagulation from a surgical standpoint.

Hepatic artery thrombosis (HAT) is a serious vascular complication of liver transplantation. Though the incidence is low (2%–9%), the risk of mortality or the need for retransplantation is as high as 50% of cases (Algarni 2015). It is important to note the current lack of consensus guidelines or comparative literature evaluating HAT prevention strategies. However, a small body of literature suggests there may be some preventative benefit to the use of antiplatelet agents or anticoagulants in the immediate postoperative period.

A retrospective study showed a decrease in HAT rates at post-transplant day 30 when patients received aspirin 325 mg daily. This group also experienced decreased graft loss related to thrombosis in the 90 days after transplantation. Notably, this population consisted of mainly cadaveric liver transplants (Shay 2013). Although reports in cadaveric liver transplantation are rare, several transplant centers worldwide describe varying anticoagulation strategies for prevention of HAT after living donor liver transplantation. Some advocate for antithrombin III administration to maintain physiologic levels, citing that diminished concentrations may contribute to a patient's hypercoagulable state (Sugawara 2002). Protocols also include unfractionated or low molecular weight heparin at prophylactic doses. Titration to maintain activated clotting time between 130 and 150 seconds has been recommended but is not universally performed (Kaneko 2005; Uchikawa 2009). This may be an important area of future research as rates of living donor transplantation increase in an effort to expand transplant opportunities.

Coagulopathy management is often a challenge in patients undergoing heart transplantation and on anticoagulation. This is not uncommon in an era of increasing indications for ventricular assist devices or other means of extra-corporeal support.

Drug Interactions with Immunosuppression

Pharmacists play a critical role in recognizing important drug interactions from commonly used immunosuppressants; these can significantly influence drug concentrations and/or efficacy and increase the risk of side effects.

Infection Prevention

As the degree of immunosuppression, and thus infectious risk, is typically highest immediately after transplantation or during active treatment for rejection, antimicrobials are often used to prevent development of active infection. As substrates of the CYP3A4 enzyme metabolism pathway, concentrations of CNIs tacrolimus and cyclosporine, as well as m-TOR inhibitors like sirolimus, are affected by the concomitant administration of azole antifungals. An azole (typically fluconazole) is often used in the perioperative period to decrease the risk of candida infections. Voriconazole is commonly chosen in lung transplant recipients to suppress growth of aspergillosis spp. As inhibitors of several CYP enzymes, including 3A4, azoles cause a decrease in metabolism and subsequent increased systemic exposure to the immunosuppressants. Many reports describe serious adverse effects as a result of this interaction, including neurotoxicity (e.g., PRES), acute kidney injury, and QT prolongation. Empiric dose reductions of CNIs or m-TOR inhibitors of up to 50% are recommended when azoles are used simultaneously. Additionally, vigilant adverse effect and therapeutic drug monitoring should take place in the initial weeks of the interaction.

Treatment of HIV Co-infection

Management of patients with HIV infection has advanced significantly in the past decade, affording them the opportunity to undergo bone marrow and solid organ transplant. Continuation of effective antiretroviral therapy and adequate immunosuppression are both important components of post-transplant care. The number of therapeutic options available and complexity of drug interactions associated with these drug classes warrants vigilant monitoring, and often proactive intervention, on the part of the pharmacist. The Department of Health and Human Services guidelines and Liverpool HIV Pharmacology group publish research and recommendations for management of these and other interactions.

As discussed previously, CNIs and m-TOR inhibitors are substrates of the CYP3A4 enzyme, and systemic exposure is affected by competing substrates, inducers, and inhibitors of this pathway. The combination of darunavir/ritonavir is currently preferred for HIV treatment-naïve patients, indicating protease inhibitors are among the most common agents used to combat viral replication. Protease inhibitors significantly inhibit 3A4 enzymes, the effect of which is a major increase in blood concentrations of the aforementioned immunosuppressants. These results occur even at standard starting doses (e.g., tacrolimus 2–4 mg twice daily) and

may ensue despite empiric dose reduction. In one case, concurrent administration of nelfinavir and tacrolimus 0.5 mg daily resulted in a trough level of 23.7 ng/mL (target level typically 4–12 ng/mL). Nelfinavir has also been shown to prolong the half-life of sirolimus by 60%. When lopinavir was added to another patient's cyclosporine-containing immunosuppression regimen, cyclosporine dose reductions of up to 75% were needed to maintain the target AUC. Increased immunosuppressant concentrations are usually seen within the first days of concomitant therapy, and doses should be preemptively decreased accordingly. Often, extending the frequency of administration so there are multiple days between doses is necessary to maintain goal levels, even in the case of drugs typically dosed twice daily (e.g., tacrolimus, cyclosporine).

In contrast to protease inhibitors, several non-nucleoside reverse transcriptase inhibitors (NNRTIs) are known to increase the rate of tacrolimus, cyclosporine, and sirolimus metabolism through induction of CYP3A4 enzymes. Reduced concentrations have been reported with concurrent use of efavirenz, etravirine, and nevirapine, though theoretical risk is present with all NNRTIs. Empiric dose adjustment is not necessarily recommended, but increased doses may be required and thus frequent monitoring should be conducted to avoid prolonging the time to therapeutic goal attainment.

The active metabolite of prednisone, prednisolone, is also metabolized through CYP3A4 enzymes. Antiretrovirals that are inhibitors or competitors of this pathway may cause prolonged systemic exposure, putting patients at heightened risk of steroid-related toxicities. No dose modifications are recommended; however, diligent monitoring for such adverse effects should be undertaken, along with utilization of the lowest possible steroid dose needed to prevent rejection.

Though less common, drug interactions between antiretrovirals and antimetabolites used for rejection prevention are also a concern. Mycophenolate mofetil, an antimetabolite commonly used in all types of transplants, is a prodrug requiring conversion to its active form, mycophenolic acid, via glucuronidation. Antiretrovirals competing for this metabolic pathway include nucleoside reverse transcriptase inhibitors abacavir and zidovudine. Though not typically part of routine therapeutic drug monitoring practices, serum concentrations of mycophenolic acid are recommended to determine if dose adjustments are needed. A similar competition occurs between azathioprine and nucleoside reverse transcriptase inhibitors didanosine and zidovudine, all of which are partially inactivated by xanthine oxidase. Little testing has been performed and evidence is limited; however, the potential increased risk of hematologic toxicities associated with azathioprine is worth close monitoring during the initiation of therapy.

Drug interactions may exist between antiretrovirals and drugs commonly used after transplant other than immunosuppression. For example, acid suppressant therapy is often started in the setting of steroid use and can significantly decrease absorption of protease inhibitors and rilpivirine, an NNRTI. Through their impact on the CPY enzyme system, azole antifungals interact with many NNRTIs and protease inhibitors. Such consequences can be significant, as in the case of ritonavir and voriconazole, the concomitant use of which can be contraindicated in certain circumstances because of sub-therapeutic concentrations of voriconazole.

When patients with HIV in the post-transplant period start or undergo adjustment of immunosuppression or antiretrovirals, careful examination of each drug combination should take place. Given the necessity of combination therapy for treatment of HIV, multiple competing drug interactions may be present. Recognition of the most potent metabolism pathway inhibitors or inducers, along with those interactions resulting in the severest of consequences, should guide prioritization of empiric dose adjustments.

A new class of antiretrovirals, integrase strand transfer inhibitors (e.g., raltegravir), offers the benefit of a reduced burden of drug interactions. Altering the antiviral regimen to incorporate these can be considered in collaboration with specialists in infectious diseases or the treatment of HIV and after the appropriate resistance testing is performed.

Treatment of Hepatitis C Virus Co-infection

Hepatitis C virus (HCV) is now the leading cause of end-stage liver disease and the primary reason for liver transplant in the United States (Alter 2007). Patients occasionally undergo transplantation before receiving treatment for HCV. They may also experience recurrent or new infection in the post-transplant period, which can damage allograft hepatocytes. In each of these cases, treatment is recommended in order to prevent fibrosis. Available regimens are evolving rapidly, as many new agents and combinations are developed and studied. Direct-acting antivirals are now preferred to the previous standard of pegylated interferon and ribavirin. Several drugs recommended in the joint American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines may interact with immunosuppression and other therapies used post-transplant. The University of Liverpool provides a comprehensive overview of these drug interactions (Table 3-1).

The NS3/A4 protease inhibitors simeprevir and boceprevir are substrates of CYP3A4 and also act as mild inhibitors of this metabolic pathway. As such, drug interactions are present when using them concurrently with CNIs and m-TOR inhibitors. Additionally, CNIs and m-TOR inhibitors are known to inhibit organic anion transporting polypeptide 1B1 (OATP1B1), which can increase circulating concentrations of NS3/A4 protease inhibitors. Simeprevir is often recommended as a component of first-line therapy for HCV treatment. After researching its effects when co-administered with cyclosporine, the combination is contraindicated because of significantly increased

Table 3-1. Drug Interactions with Immunosuppressants in Patients Undergoing Treatment for HIV and HCV

Agent	Immunosuppressant	Interactions	Therapeutic Considerations
Azole antifungals			
Fluconazole Itraconazole Voriconazole Posaconazole	CNIs m-TOR inhibitors	Inhibition of CNI, m-TOR inhibitor metabolism	Empiric dose decrease of 50% or more for CNIs, m-TOR inhibitors
Protease inhibitors			
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir	CNIs m-TOR inhibitors	Inhibition of CNI, m-TOR inhibitor metabolism	Empiric dose decrease of 75% or more for CNIs, m-TOR inhibitors
NNRTIs[a]			
Efavirenz Etravirine Nevirapine	CNIs m-TOR inhibitors	Induction of CNI, m-TOR inhibitor metabolism	No empiric dose adjustments, increased frequency of monitoring
NRTIs			
Abacavir Zidovudine	Mycophenolate mofetil	Competitive inhibition of glucuronidation of mycophenolate mofetil to mycophenolic acid	No empiric dose adjustments, consider monitoring concentrations of mycophenolic acid
Didanosine Zidovudine	Azathioprine	Competitive inhibition of xanthine oxidase metabolism	No empiric dose adjustments, monitor for hematologic toxicities
NS3/A4 Protease Inhibitors			
Simeprevir Boceprevir	CNIs m-TOR inhibitors	Inhibition of CNI, m-TOR inhibitor metabolism; inhibition of NS3/A4 metabolism[b]	Recommendations vary, see text for details
Ombitasvir/paritaprevir/ritonavir	CNIs[c]	Inhibition of CNI metabolism	Empiric dose adjustments 80% or more of CNIs

CNI = calcineurin inhibitor; HCV = hepatitis C virus; m-TOR = mammalian target of rapamycin; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor

[a]Risk theoretically conferred with all NNRTIs.

[b]Metabolism occurs through organic anion-transporting polypeptide 1B1

[c]Interaction theoretically possible with m-TOR inhibitors due to similar metabolic pathways

Information from National Institute of Health. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents; The Liverpool HIV Pharmacology Group; American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitic C; and the University of Liverpool.

exposure to both drugs. Experience with the use of tacrolimus and NS3/A4 protease inhibitors has been varied. Little effect on metabolism was seen when using tacrolimus and simeprevir together; however, significant dose adjustments were needed to avoid supratherapeutic tacrolimus levels when administered with boceprevir. Little has been reported about how sirolimus concentrations are affected by simeprevir or boceprevir, but existing reports suggest they may be either increased or decreased.

Paritaprevir is another protease inhibitor that requires ritonavir boosting and is co-formulated with ombitasvir as an alternative treatment for certain patients with HCV. The paritaprevir/ritonavir components are strong inhibitors of CYP3A4 and can significantly elevate trough levels of tacrolimus (25-fold) and cyclosporine (15-fold). Starting doses of tacrolimus 0.5 mg weekly or one-fifth the usual daily dosage of cyclosporine are recommended to avoid serious adverse effects. Although concomitant use of paritaprevir/ritonavir and m-TOR inhibitors has not been studied, the nature of sirolimus and everolimus metabolism suggests that systemic exposure may be increased, and thus close laboratory monitoring of trough concentrations and use of a conservative starting dose is warranted.

Because of the rapidly changing nature of HCV treatment, options for therapy that eliminates concerning drug interactions may be possible. Sofosbuvir, an NS5B nucleotide polymerase inhibitor, is a p-glycoprotein substrate with no effect on the CYP enzyme system. Daclatasvir is an NS5A inhibitor metabolized by CYP3A4, but in studies it did not show clinically relevant impact on concentrations of other 3A4 substrates. These may be viable treatment options, alone or in combination, for many HCV-infected individuals, and could be recommended in consultation with a specialist.

As with the previously discussed antiretroviral agents, drug interactions may be present between medications used to treat HCV and those for infection prevention. Specifically with azole antifungals, this arises from effects on CYP enzymes. For post-transplant patients starting new therapy for HCV in the setting of prophylactic antimicrobials, careful evaluation of associated risks should guide therapy decisions in both realms. Also, the use of antivirals that inhibit or compete for metabolism via 3A4 enzymes has the potential to increase steroid-related toxicities, and thus consideration must be given to using the lowest steroid dose necessary to prevent allograft rejection.

CONSIDERATIONS IN NEUROSURGERY

General Concepts

Cerebrovascular Hemodynamics

The cranium is an enclosed space comprising the brain, cerebrospinal fluid (CSF) and blood. Brain tissue requires constant perfusion that is tightly regulated to maintain its supply of oxygen and glucose. Cerebral perfusion pressure (CPP) is a surrogate target for maintaining adequate cerebral blood flow (CBF= blood supply to the brain over any period). The CPP is defined as MAP minus the intracranial pressure (ICP); hence, CPP is directly related to MAP and inversely related to ICP (Table 3-2).

A CPP range of 60–80 mm Hg is the normally accepted target, indicating the pressure that is required to maintain adequate cerebral blood flow and to avoid neuronal death. Cerebral autoregulation enables the brain to maintain CBF over a variety of blood pressures ranges (MAP or CPP). Autoregulation primarily involves increasing or decreasing brain's arterial vascular resistance in order to maintain regional or global blood flow to the brain (Figure 3-1). It is important to note that loss of cerebral autoregulation can be seen after severe brain injury. In an injured brain, the relationship between CBF and blood pressure becomes linear because of the loss of autoregulation. The injured brain becomes even more susceptible to neuronal death. Therefore, patients with brain injury require tight control of blood pressure (MAP or CPP) after brain injury.

The range of normal ICP is 5–15 mm Hg. An increase in ICP can lead to a decrease in CPP and brain tissue damage.

Table 3-2. Cerebrovascular Hemodynamics

		Normal range
MAP	Mean arterial pressure (2/3 × diastolic BP + 1/3 × systolic BP)	65–85 mm Hg
ICP	Intracranial pressure[a]	5–15 mm Hg
CPP	Cerebral perfusion pressure = MAP – ICP	>70 mm Hg

[a]Requires an invasive catheter for measurement (i.e., EVD catheter or ICP bolt).

BP = blood pressure.

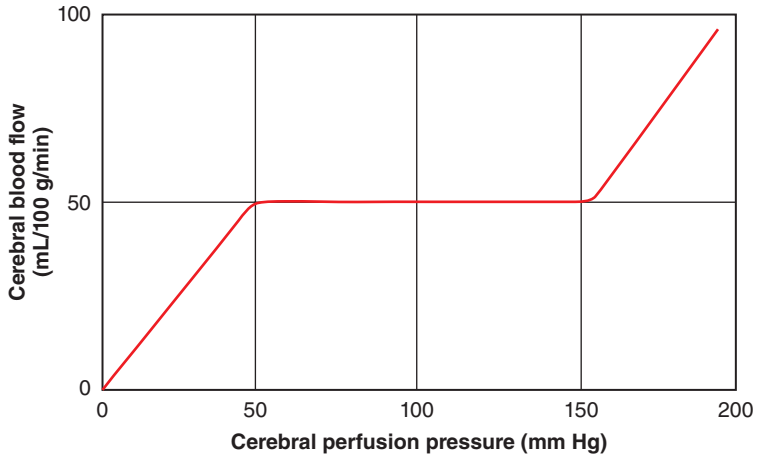

Figure 3-1. Cerebral blood flow is directly correlated with MAP and CPP. The autoregulation curve demonstrates that in a healthy brain cerebral blood flow is tightly maintained despite fluctuations in MAP and CPP (range 50 – 150 mm Hg). A MAP and CPP outside of the autoregulation capacity will have a significant effect on CBF.

Information from Hall JB, Schmidt GA, Kress JP. Principles of critical care, ed 4. New York, NY: McGraw-Hill, 2015.

Any interruption or additional space occupying mass will cause a rise in ICP. Causes for increased brain volume include brain hemorrhage, a space occupying lesion (e.g., tumor) or blockage of CSF flow. An extraventricular drain (EVD) is the gold standard monitoring device for ICP. An EVD allows drainage of CSF, whereas other modalities (e.g., ICP bolt, epidural monitoring) only measure ICP.

The decision to monitor ICP is usually based on the underlying reason for increased ICP and its likely progression (Le Roux 2014). Indications for placement of an ICP monitor are less well defined for conditions other than traumatic brain injury (TBI) (BTF 2007). Clinicians generally use their clinical judgment when determining whether a patient will benefit from ICP monitoring for conditions other than TBI. The accepted treatment threshold for elevated ICP is greater than 15 or 20 mm Hg; this is based on limited evidence (BTF 2007).

A recent Latin American multi-center trial found no benefit in survival and functional outcomes at 3 months when comparing protocolized care with ICP monitoring versus treatment based on imaging and clinical examination in TBI patients (Chesnut 2012). The study was important in highlighting the limitations of ICP monitoring, stressing that the exact physiologic number may not be more important than clinical signs of elevated ICP. However, ICP monitoring continues to be the primary mode of surgical treatment for a spectrum of neurologically injured patients. A discussion of the risks vs. benefits of ICP monitoring is beyond the scope of this chapter.

A rapid rise in brain volume can lead to a marked rise in ICP, which will ultimately lead to compromised CPP. The interventions for maintaining CPP in an acutely brain injured patient include reducing ICP or increasing MAP to maintain CBF. Medical interventions for reducing ICP are discussed in section on intracranial hypertension and herniation.

Blood Pressure Control

Blood pressure should be treated as a moving target in neurocritical care because the primary goal in a neurologically injured patient is to avoid neuronal death by maintaining CPP and ultimately cerebral blood flow. Patients with cerebral vasoconstriction or high ICP may require a higher MAP target because blood pressure is directly related to CPP. Meanwhile, patients with an acute brain hemorrhage require strict systolic blood pressure (SBP) control, with a target SBP of less than 140 mm Hg in order to avoid secondary brain injury (Anderson 2013; Hemphill 2015). Hence, the blood pressure target varies based on presenting neurologic injury and progression, and must be individualized. For example, a patient presenting after aneurysmal subarachnoid hemorrhage (aSAH) will have a target SBP of 100–140 mm Hg during initial presentation. However, once the aneurysm has been surgically treated, the SBP target can be liberalized to 100–200 mm Hg in order facilitate cerebral perfusion. Reflex hypertension can be seen during vasospasm period (4–21 days after subarachnoid hemorrhage) as a natural response to maintain CPP in order to counter increased cerebral arterial pressure from vasospasm. It is prudent to discuss the target blood pressure range daily for each patient admitted to a neurocritical care unit based on their underlying disease state and clinical condition.

Glucose Management

Neurologically injured patients can experience significant stress-induced hyperglycemia during initial

Table 3-3. Target Blood Glucose and Treatment Thresholds

	Treatment Threshold	Blood Glucose Target Range
American College of Critical Care Medicine	> 150 mg/dL	< 150 mg/dL (trauma) ≤ 180 mg/dL (stroke[a])
Surviving Sepsis Campaign 2012	> 180 mg/dL	≤ 180 mg/dL
Subarachnoid Hemorrhage Guidelines (NCS)	Not specified	≤ 200 mg/dL
Acute Ischemic Stroke (AHA)	Not Specified	140–180 mg/dL
Standards of Medical Care in Diabetes	> 180 mg/dL	140–180 mg/dL

[a]Ischemic stroke, intraparenchymal hemorrhage, aneurysmal subarachnoid hemorrhage or traumatic brain injury.

NCS= Neurocritical Care Society, AHA=American Heart Association.

Information from Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012;40: 3251-76; Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637; Diringer MN, Bleck TP, Hemphill JC III, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care 2011;15:211-40; Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947; and American Diabetes Association. Standards of Medical Care in Diabetes 2016;39:Suppl 1:S99-104.

presentation to the ICU. Patients with a history of diabetes are at an increased risk of developing hyperglycemia while in the ICU. Hyperglycemia is associated with increased mortality and worse functional outcomes after ischemic stroke, intracerebral hemorrhage, aSAH, and TBI. Insulin infusion is the preferred method of treatment for hyperglycemia in the ICU (Jacobi 2012). Treatment threshold and blood glucose targets are controversial and vary among guideline recommendations (Table 3-3).

A practical approach to glucose management in the ICU is to implement an infusion protocol with proven safety in the critically ill patient population. The treatment threshold and insulin infusion titration should be well defined. Stable patients (especially patients that are eating meals while in the ICU) can be transitioned to subcutaneous insulin. Careful attention should be given to transitioning patients from insulin infusion to subcutaneous insulin dosing when appropriate (ADA 2016). Optimal transition regimens (preferred basal-bolus regimen) based on patient's dietary status (eating meals vs. continuous enteral nutrition) should be clearly outlined within the insulin protocol. Tight blood glucose control has not been proven beneficial; blood glucose targets less than 110 mg/dL should be avoided.

Venous Thromboembolism Prophylaxis

Initiating thromboembolism prophylaxis can be a daunting task in the neurologically injured patients because risk of developing venous thromboembolism (VTE) must be balanced with the risk of brain hemorrhage. In the absence of underlying coagulopathy, VTE prophylaxis can be initiated 24–48 hours after the surgical procedure or after two consecutive stable CT scans for most patients (Gould 2012; Nyquist 2016).

Acute Coagulopathy Reversal in Hemorrhagic stroke

It is imperative for the critical care pharmacist to understand the principles of coagulopathy reversal in order to facilitate surgical management in neurologically injured patients. Patients presenting with a neurological injury may require acute coagulopathy reversal because of acute hemorrhage or an urgent reversal before surgery to reduce damage from ongoing bleeding.

Unfractionated Heparin and Low-Molecular-Weight-Heparins

Protamine sulfate should be administered in the event of acute intracranial hemorrhage while on therapeutic unfractionated heparin or low-molecular-weight heparin (LMWH) doses. Reversal with protamine sulfate is not recommended for patients receiving prophylactic therapy (Table 3-4). The maximum one-time dose of protamine is 50 mg. Administration of large doses of protamine may exacerbate bleeding because protamine itself is a weak anti-coagulant. Protamine has a short half-life (about 5 minutes) compared with heparin (1–2 hours) and LMWH (2–8 hours, longer with renal dysfunction). Rebound anticoagulant effect may be seen with large doses of heparin infusion and subcutaneous administration of LMWH. Repeat dosing of protamine may be indicated based on elevated laboratory parameters (i.e., elevated aPTT 3 to 4 hours

Table 3-4. Protamine Sulfate Dosing

	Initial Dose	Repeat Dose
UFH[a]	1 mg per 100 international units	0.5 mg per 100 international units
Enoxaparin	1 mg per 1 mg of enoxaparin (if administered within 8 hours) 0.5 mg per 1 mg of enoxaparin (if administered within 8 12 hours)	0.5 mg per 1 mg of enoxaparin
Dalteparin/ tinzaparin	1 mg per 100 anti-Xa units	0.5 mg per 100 anti-Xa units

UFH = unfractionated heparin.

[a]Dosed based on preceding 2–3 hours of UFH administration, repeat doses should be based on elevated aPTT.

Information from Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6-46.

after protamine administration). A repeat dose of protamine can be administered if clinical bleeding persists with LMWH administration. Protamine administration is associated with anaphylaxis, bradycardia, bronchoconstriction, and hypotension. These adverse effects can be mitigated by slowing the infusion rate to less than 5 mg/minute and pre-medicating with an anti-histamine and corticosteroid (Frontera 2016).

Antiplatelet Agents

There is limited evidence demonstrating clinical benefit with transfusion of platelets for patients with intracranial hemorrhage while on anti-platelet therapy. The guidelines for anti-thrombotic reversal recommend one single-donor apheresis unit of platelets in patients with intracranial hemorrhage that will undergo a neurosurgical procedure. A number of platelet function assays (PFAs) are now available to assess the effect of antiplatelet therapy. Platelet function assays should be obtained at baseline to assess the need for platelet transfusion. The test can also be obtained 1 hour after platelet transfusion to assess the need for repeat transfusion. The guidelines state that it is reasonable to administer one unit of platelets for patients undergoing a neurosurgical procedure in the absence of PFAs. An additional transfusion of platelets can be considered based on repeat PFA and clinical picture. Platelet transfusion is not recommended in nonsurgical patients. The risks associated with platelet transfusion include: transfusion-related acute lung injury (TRALI), thrombosis, disseminated intravascular coagulopathy (DIC), hemolytic transfusion reactions, and transfusion-associated sepsis (Baron 2013; Pakala 2011; Frontera 2016).

Desmopressin is a vasopressin analog that works by increasing levels of factor 8 and von Willebrand factor leading to secondary improvement in platelet adhesion. A one-time dose of desmopressin 0.4 mcg/kg can be administered in patients with intracranial hemorrhage while on anti-platelet therapy. It has a relatively quick onset of action: the effect can be seen within 30 minutes and lasts up to 4 hours. Desmopressin is associated with tachyphylaxis; therefore, a repeat dose is not recommended (Frontera 2016).

Anticoagulants

Intracranial hemorrhage results in significant morbidity and mortality and is always considered a life-threatening emergency. The guidelines for antithrombotic reversal recommend administration of four-factor PCC (4FPCC) over fresh frozen plasma (FFP) for warfarin-induced intracranial hemorrhage. Success of reversal with 4FPCCs can be reliably assessed within 15–30 minutes after the infusion. The goal INR for reversal for patients with intracranial hemorrhage is less than 1.4. Vitamin K (or phytonadione) 10 mg by intravenous route should also be administered in these patients for sustained reversal. A rebound coagulopathy can be seen 6 hours after 4FPCC administration if vitamin K is not administered concomitantly. If warfarin needs to be reversed because of a planned surgical procedure (≥ 48 hours apart), a conventional approach to reversal should be utilized (i.e., holding warfarin and/or administering vitamin K enterally). Vitamin K should be administered intravenously (slow infusion ~30 minutes to reduce risk of anaphylactoid reaction) in emergent situations.

The INR reversal rates are similar when comparing intravenous to enteral administration of vitamin K 24 hours after the administration (Lubetsky 2003). Therefore, in non-urgent situations, warfarin can be administered enterally. A history of heparin-induced thrombocytopenia (HIT) is a contraindication to 4FPCC administration, because this product contains a small amount of heparin. Administration of three-factor PCC Profilnine SD plus FFP can be considered in patients

with a confirmed history of HIT. Profilnine SD is a 3-factor PCC that does not contain heparin, however, FFP should be administered concomitantly to provide therapeutic levels of factor 7. It should be noted that 3-factor PCCs do not have FDA label approval for warfarin-associated coagulopathy, and this is an off-label use recommendation in a special patient population. The primary concern with administering PCCs is prothrombotic complications such as formation of new thrombus and DIC (Baron 2013; Holbrook 2012; Nutescu 2013; Frontera 2016).

Idarucizumab is now available for dabigatran reversal for patients presenting with acute hemorrhage. Reversal is recommended for patients with acute intracranial hemorrhage with dabigatran administration within the last 2 days. The half-life of dabigatran is prolonged (up to 7 days) in patients with poor renal function caused by drug accumulation. Therefore, in patients with renal insufficiency, reversal should be attempted for patients who consumed dabigatran more than 48 hours before presentation. Activated PCCs (aPCCs) 50 international units per kg can be used for dabigatran reversal in the absence of idarucizumab. Additionally, activated charcoal (50 g) can be administered for patients presenting within 2 hours of ingestion (Frontera 2016).

Activated PCCs or 4FPCCs can be used for reversal in patients with acute intracranial hemorrhage while on oral anti-Xa inhibitors (rivaroxaban, apixaban and edoxaban). The recommended dose is 50 international units per kg for both products (aPCCs and 4FPCCs). Because of the lack of a specific reversal agent, it may be prudent to develop a hospital-based protocol for acute life-threatening reversal with preferred agents outlined for use. This information should be disseminated hospital wide and be made readily available. Patients with intracranial hemorrhages should receive reversal therapy in the shortest possible time that allows safe administration (Nutescu 2013). Activated charcoal (50 g) can be administered for patients presenting within 2 hours of ingestion (Frontera 2016).

Seizures

Seizure prophylaxis

Traumatic brain injury is currently the only presenting condition in the neuro-ICU where prophylactic therapy has reduced the incidence of early seizures. The recommended duration of prophylactic therapy in patients with TBI is 7 days (Table 3-5). Because of a favorable safety profile of levetiracetam, compared with the first-generation antiepileptics, there has been an increase in the use of prophylactic therapy for a large spectrum of patients (Rowe 2014). There are limited data evaluating harm from short-term seizure prophylaxis in neurologic conditions in which the efficacy of seizure prophylaxis has not been definitively proven.

Seizure prophylaxis can also be considered for patients presenting with aneurysmal subarachnoid hemorrhage (aSAH). Guidelines recommend against using phenytoin for seizure prophylaxis in patients with aSAH. Recent studies have suggested that administration of phenytoin for seizure

Table 3-5. Summary of Seizure Prophylaxis Recommendations

Neurological Conditions	Prophylaxis Recommended	AED	Duration
Intracerebral tumors	No	-	-
Traumatic brain injury	Yes	Phenytoin or Levetiracetam	First 7 days after injury
Subarachnoid hemorrhage[a]	Unclear	Levetiracetam, Carbamazepine or Valproic Acid	Short duration (3-7 days)
Craniotomy (e.g., for AVM)	No	-	-
Ischemic stroke	No	-	-
Intracerebral hemorrhage	No	-	-

[a]It is unclear whether prophylaxis should be used. Phenytoin should not be used for prophylaxis in aSAH.

Infromation from Rowe AS, Goodwin H, Brophy GM, et al. Seizure prophylaxis in neurocritical care: a review of evidence-based support. Pharmacotherapy 2014;34:396-409.

AED = anti-epileptic drug; AVM = arteriovenous malformation.

prophylaxis in patients with aSAH may be associated with worse long-term outcomes (Diringer 2011).

Treatment of Perioperative Seizures

Patients who experience seizures perioperatively may be treated according to general management of epilepsy guidelines (Brophy 2012). The most common type of perioperative seizure is a focal or generalized tonic-clonic seizure. There is a paucity of data regarding the duration of treatment with antiepileptics if the patient has a seizure on presentation or intra-operatively. Generally, clinicians recommend continuing anti-epileptic therapy throughout the inpatient stay or up to 4 weeks. A decision to continue therapy can also be deferred until the first outpatient follow-up with a neurosurgeon.

Considerations for Analgesia and Sedation

Postoperative Pain

Management of postoperative pain is a priority for all patients admitted to the neurosurgical care unit. Poor pain control is associated with poor patient satisfaction and has been associated with posttraumatic stress disorder (most commonly seen in trauma or burn patients) (Levenson 2007). Poorly treated acute pain can also lead to chronic pain. Most patients admitted to the ICU are not able to communicate their pain because of altered level of consciousness; this is especially common in the neurologic ICU. It is vital to use the critical care pain observation tool (CPOT) or behavioral pain scale (BPS) for appropriate detection of pain in mechanically ventilated patients (Barr 2013). Pain and discomfort should be assessed at least 2–3 times daily in intubated patients that are not receiving continuous infusion opioid therapy. The need for pain management should be anticipated based on presenting illness and type of surgical procedure.

All patients admitted postoperatively should have tiered or "as needed" pain medication orders for moderate and severe pain. Pain orders can also be placed using moderate or severe pain scores treatment range (e.g., moderate pain score 5 to 7 and severe pain > 7 on a 10-point pain score). Clearly defining pain orders can aid in prompt administration of pain medications. A prior history of chronic pain should be taken into consideration, and doses should be increased accordingly. Neurologically intact patients can be placed on patient-controlled anesthesia (PCA) pumps postoperatively. The need to transition to an as-needed regimen should be assessed daily for patients on PCA. Patients should only be transitioned off PCA once adequate pain control has been achieved. Pharmacists have an opportunity to play a key role in determining transition therapy because patients need to be transitioned to an IV or enteral regimen based on equianalgesic dosing. A reduction of dose by about 20% is recommended when switching between opioids. Patients should be transitioned to a stable oral pain regimen when feasible, in order to facilitate discharge planning.

Sedation in a Neurologically Injured Patient

Sedation in a patient with neurologic injury can be challenging because most patients present with altered mentation. This also presents a challenge for monitoring and titration of sedation. Facilitation of mechanical ventilation is the primary reason patients may need sedation in the ICU. It is imperative to assess the etiology of agitation before initiating a sedative infusion. Some of the underlying causes of agitation include pain, delirium, hypoxemia, hypoglycemia, hypotension, or withdrawal from alcohol and other drugs.

The doses of sedative medications can be significantly reduced by ensuring adequate treatment of the underlying cause of agitation. An analgo-sedation (analgesia before sedation) strategy is preferred and should always be used because the primary cause of agitation for most postoperative patients is pain. It is imperative to provide a definitive goal of therapy before initiation of sedation based on Richmond Agitation sedation score (RASS) or Ramsay Sedation Score (RSS). Light sedation (RASS score of 0–2, RSS score of 3–4) is preferred for critically ill patients. Application of these scales may be limited in the neurologic ICU. For example, a patient with eyelid opening apraxia may be alert and calm but might be scored as a 4 on RASS score because of the inability to open his/her eyes. Neurologically injured patients may also have fluctuating mental status based on their clinical presentation not related to sedative administration, which makes it difficult to titrate sedation in this patient population.

Clearly defined goals for sedation based on monitoring tools aid in limiting toxicities associated with sedatives even with their limitations in application (Barr 2013; Seder 2015). It is also important to avoid titrating sedation solely based on hyperdynamic fluctuations in patients with suspected paroxysmal sympathetic hyperactivity (PSH) (Baguley 2014). Patients with PSH may seem restless because of hyperdynamic fluctuations. Medical treatment for PSH should be initiated instead of increasing sedation for presumed agitation in these patients (Samuel 2016).

Patients admitted to the neurologic ICU often require an assessment of mental status to assess the progression of their disease process and/or recovery. Dexmedetomidine inhibits the patient's ability to communicate to a lesser degree in comparison to propofol (Jakob 2012). Dexmedetomidine may be the preferred agent in mechanically ventilated neurologically injured patients requiring short-term light sedation. Robust evidence recommending its use as a first-line agent is lacking. A caveat to using dexmedetomidine in the neurosurgical patient population is its lack of anti-epileptic properties. Therefore, it should not be used in patients with a high suspicion of seizures (i.e., alcohol withdrawal) or status epilepticus.

Patients in the neurologic ICU may also receive continuous infusion sedatives for indications other than facilitating mechanical ventilation (e.g., management of refractory status epilepticus [RSE], refractory ICH post-TBI). These patients require a deeper level of sedation or medically induced coma. Midazolam and propofol are the preferred agents for deep sedation. Pentobarbital may be reserved as a last-line agent for medically induced coma. Sedatives are titrated in these specific clinical scenarios based on the clinical indication. In patients requiring continuous infusion sedative for management of RSE, the goal of therapy is seizure cessation. Therefore, sedatives should be titrated on the basis of a burst suppression pattern on the electroencephalography (EEG) or bispectral index (BIS) monitor. If deep sedation strategy is being used, sedatives should be tapered off slowly and cautiously once the underlying disease has been controlled. Abrupt withdrawal of sedation can result in rebound ICP crisis or break through seizures. It is important to note that sedation interruption is not recommended for these patients until the underlying disease state has been appropriately treated.

Intracranial Hypertension and Herniation

Intracranial hypertension is defined as persistent (> 5 minutes) elevation of ICP above 20 mm Hg. Brain herniation occurs when the compensatory mechanisms have been overwhelmed, leading to displacement or compression of the brain stem, cranial nerves, or cerebral vasculature. Brain herniation can occur independently; however, it is often linked to intracranial hypertension. Detection of intracranial hypertension requires invasive monitoring but it can also be detected based on clinical signs (headache, nausea, and vomiting or altered mental status accompanied with physical signs of hypertension, bradycardia and apnea) before device placement (Stevens 2015). Intracranial hypertension and herniation are medical emergencies and should be treated as "Brain Code" according to Neurocritical Care Society. It is imperative to initiate resuscitative measures as soon as possible, because this is a medical emergency.

Brain Code General Management

The Neurocritical Care Society has recommended a tiered approach to resuscitative methods during a "Brain Code" (Table 3-6). Higher tiers represent more aggressive management and is associated with a higher risk of complications. Tier zero therapies include: elevating the head of bed to greater than 30 degrees, treatment of hyperthermia, hyponatremia, and initiation of high-dose corticosteroids (e.g., dexamethasone 10 mg bolus followed by 4 mg every 6 hours, for vasogenic edema from brain tumors). First-tier therapies include initiation of hyperosmolar therapy such as mannitol or hypertonic saline (HTS), placement of external ventricular drainage and hyperventilation to a $PaCO_2$ of 30–35 mm Hg (usually effective for ≤ 2 hours).

Second-tier therapies include elevation of serum sodium and sedation. The target for serum sodium is dependent on patient's physiologic conditions. Serum sodium greater than 160 mmol/L should be avoided. Agitation can lead to increased ICP, thus deep sedation with fentanyl or remifentanil in addition to propofol should be used.

In patients where all measures fail, tier 3 may be considered to avoid herniation. Tier 3 therapies include pentobarbital coma and therapeutic hypothermia. Pentobarbital can be used for medically induced coma. It is usually administered via continuous infusion after a bolus dose. Bolus dose is typically 10–20 mg/kg administered over 30 minutes followed by continuous infusion of 1–5 mg/kg/hr. Pentobarbital therapy is usually a last-line measure because hemodynamic instability associated with its use can cause a myriad of adverse events. Concomitant administration of vasopressor therapy is often required to maintain MAP. Other adverse events include gut ischemia leading to ileus. It is usually a last-line measure because hemodynamic instability associated with its use may lead to acute kidney injury, severe metabolic abnormalities, and multi-organ failure.

It is important to recognize that medical therapy is usually a temporizing measure in treatment of refractory intracranial hypertension. Placement of EVD for removal of CSF

Table 3-6. Tiered Therapy for Management of Intracranial Hypertension

Tier 0	Standard measures: assessment of circulation, airway and ventilation, head of bed > 30°, dexamethasone for vasogenic edema
Tier 1	Hyperosmolar therapy: mannitol or hypertonic saline
Tier 2	Elevation of serum sodium and sedation (propofol)
Tier 3	Pentobarbital, hypothermia

Information from Stevens RD, Shoykhet M, Cadena R. Emergency neurological life support: intracranial hypertension and herniation. Neurocrit Care 2015;23(Suppl 2):76–82.

or decompressive surgery is usually needed to for definitive management of intracranial hypertension and prevention of herniation. Refractory ICP is a serious condition that can carry a grave medical diagnosis. Medical teams may consider including the palliative care team to discuss benefit and risks associated with tier 3 therapies and goals of care with family members at this stage (Brophy 2015; Stevens 2015, Marshall 2010).

Hyperosmolar Therapy Overview

Mannitol is an osmotic diuretic that draws water out of the brain within minutes of administration. It is available as 25% intravenous vials or 20% intravenous solution. The usual dose is 0. 25–1 g/kg as a bolus and may be repeated hourly, if needed.

Mannitol's therapeutic effect is dependent on the presence of an osmolarity gradient that enables water movement out of the brain via osmosis. If accumulated, mannitol can worsen cerebral edema. Therefore, it is important to calculate an osmolarity gap in addition to serum osmolarity before repeat dosing. An osmolarity gap of greater than 20 mOsm/kg is indicative of incomplete mannitol clearance and potential for reverse osmotic shift and nephrotoxicity. Osmolarity gap can be calculated by subtracting calculated osmolarity [(2 × (sodium + potassium)) + (blood urea nitrogen / 2.8) + (glucose / 18)] from measured serum osmolarity. Isolated elevated serum osmolarity (> 320 mOsm) is not a contraindication to receiving mannitol therapy; instead the osmolarity gap should be used to guide therapy. Adverse effects associated with mannitol administration include: acute tubular necrosis, hypernatremia, hypokalemia and hypotension caused by diuresis (Brophy 2015).

Currently, HTS is available as 1.5%, 2%, 3%, 5% for continuous infusion, and 23.4% for bolus administration. It exerts its therapeutic effect in a manner similar to mannitol; by drawing water out of the brain from an increased osmolarity gradient based on acute rise in sodium concentration. The advantage of HTS is that it does not cross the blood-brain barrier and keeps water in the intravascular space with the additional benefit of increasing MAP and CPP. The most common side effect associated with HTS is fluid overload, which is more commonly seen with continuous infusion in patients with congestive heart failure.

Use of a central line is recommended for administration of HTS at concentrations greater than 2% in order to avoid extravasation. Previous studies have reported lack of extravasation when administering 3% and 7.5% HTS boluses by a peripheral line in emergency situations; however, caution must be exercised. Patients can be initiated on HTS continuous infusion at 1 ml/kg/hour with a serum sodium goal concentration of 145–155 mEq/L (Brophy 2015; Stevens 2015). Repeat serum sodium should be obtained three to four times a day in order to achieve the goal concentration and to avoid a precipitous rise in serum sodium concentration.

Use of HTS seems to be more beneficial for management of ICP crisis in patients presenting with TBI because of its positive effect on MAP and CPP. Mannitol would be the preferred agent in patients who do not have a dedicated central intravenous line for administration or with a history of congestive heart failure.

Infectious Complications

Guidelines for surgical prophylaxis recommend a single agent (cefazolin, clindamycin or vancomycin) for management of clean surgical procedures (i.e., EVD placement, craniotomies, and CSF shunt placement). Cefazolin is the preferred agent for surgical prophylaxis. Clindamycin or vancomycin can be used in patients with β-lactam associated allergy.Vancomycin should be used in patients with a history of methicillin-resistant organisms (Bratzler 2013).

Extraventricular drain placement is the most common neurosurgical intervention in the ICU; it can aid in relieving acute pressure, draining CSF, and monitoring ICP. An EVD placement can often result in immediate improvement of neurologic status because of reduced ICP and improved cerebral perfusion. An EVD placement does carry a risk of ventriculitis. Antimicrobial-coated EVD catheters are associated with a reduced risk of infection. A single dose of antibiotic is recommended to be administered before the procedure for infection prevention. Continuing prophylactic antibiotic therapy while EVD is in place has not proved beneficial in reducing the infection rate. The strongest predictor of developing ventriculitis is EVD manipulation. Withdrawal of CSF and EVD manipulation should be minimized to reduce the risk of infection (Fried 2016).

If a patient develops ventriculitis or CSF shunt infection, broad-spectrum antibiotics should be initiated. Empirical coverage of nosocomial organisms (i.e., pseudomonas and MRSA) is imperative. Antibiotics with excellent penetration into the CSF should be used for treatment. Therapy should be narrowed once the infective organism is identified. Source removal (EVD/shunt replacement) is the most important intervention for management of these invasive infections.

Postoperative Care in Special Populations

Aneurysmal Clipping or Coiling

Aneurysmal SAH is a serious condition that requires immediate neurosurgical intervention to prevent rebleeding. In addition to the primary injury caused by brain hemorrhage, patients with SAH are at risk of secondary brain injury from delayed cerebral ischemia (DCI) up to 21 days after injury. Therefore, patients with SAH typically have a longer ICU stay, due to their need to be monitored closely during the vasospasm window (peak incidence 4–14 days post bleed). Blood pressure management goals differ in SAH patients based on their progression into the disease and presence of DCI. Upon initial presentation to the ICU "tight" blood pressure control, typically SBP 100–140 mm Hg, is recommended to

prevent rebleeding. In contrast, once the aneurysm has been surgically treated (clipped or coiled), it is recommended to liberalize blood pressure to facilitate cerebral perfusion.

Vasospasm is narrowing of the irritated cerebral arteries caused by the presence of blood. Vasospasm increases cerebral vascular resistance and compromises cerebral blood flow. Sustained vasospasm can lead to ischemic injury (i.e., DCI) and neuronal death. Nimodipine (60 mg orally every 4 hours) is indicated for all patients with SAH. Administration of nimodipine in SAH was associated with improved outcome, possibly by limiting DCI. Some patients may not be able to tolerate nimodipine because of its effect on blood pressure. A reduced dose of nimodipine (30 mg every 2 hours) can be used in these patients, although complete benefit may not be seen with reduced dose strategy (Sandow 2015).

Delayed cerebral ischemia is a clinical diagnosis and can be difficult to detect; CT angiography and CT perfusion are needed for definitive diagnosis. Therapeutic management of DCI is induced hypertension (or hemodynamic augmentation). This means increasing MAP (often 85–110 mm Hg) in order to raise CPP to overcome cerebral vascular resistance secondary to vasospasm and facilitate CBF. Patients often require high dose vasopressor therapy for hemodynamic augmentation in order to prevent ongoing ischemic injury. It is recommended to review SBP and MAP target range daily in SAH patients. Overall hemodynamic parameters should be clearly defined when targeting supratherapeutic MAP goals (i.e., optimization of cardiac index and central venous pressure).

Administration of aminocaproic acid was associated with reduced rebleeding rates in a retrospective analysis. The benefit associated with antifibrinolytic therapy may have been more pronounced historically because of a delay in surgical management of aneurysm. Diagnostic angiography can be scheduled within 24 hours at most high-volume comprehensive stroke centers, which makes the benefits from aminocaproic acid less attainable. An early, short course, continuous infusion can be considered for up to 72 hours or until planned surgical intervention, whichever is shorter. It may be more prudent to administer aminocaproic acid if a delay in surgical treatment is expected (e.g., difficult location of aneurysm, stent-assisted coiling planned). A recent history of thrombosis (MI and/or DVT) should be considered as a relative contraindication to aminocaproic acid. The recommended dose of aminocaproic acid is a 4 g loading dose administered over 1 hour, followed by a continuous infusion of 1 g/hour for a maximum of 72 hours. The continuous infusion should be discontinued 2– 4 hours before CT angiography (Diringer 2011).

Antiplatelet Therapy for Endovascular Intervention

Neuroendovascular stent placement is becoming increasingly common because of its relatively noninvasive approach. Neurosurgical stents are associated with high risk of thrombosis peri-procedurally (up to 20%). The most common neurointerventional procedures requiring dual anti-platelet therapy (DAT) include: elective coil embolization of aneurysms, stent-assisted coil embolization, and flow-diverting stents. Aspirin with clopidogrel is the most common DAT used. Dual anti-platelet therapy in these patients should be optimized because of the high risk of thrombosis during the procedure and the possibility of clopidogrel resistance.

Commercially available platelet function assays (PAF-100 and VerifyNow) can aid clinicians in determining the degree of resistance to DAT for patients peri-procedurally. VerifyNow, the most commonly used test to determine platelet reactivity in neuroradiology, is a point of care test that reports platelet functionality in P2Y12 reactivity units (PRUs). Higher units correspond to a lower level of P2Y12 inhibition and higher risk of thrombosis. Consequently, a lower PRU value means a higher level of inhibition and thus a low chance of thrombosis. The risk of thrombosis should be balanced with the risk of intracerebral hemorrhage. There is a paucity of data regarding the optimal range for VerifyNow test for neurointerventional procedures because most of the evidence has been translated from cardiology. Consensus statements recommend a PRU range of 95–230 PRUs for flow-diverting stent placement (Gandhi 2014).

Management of Organ Donors in the ICU

In patients meeting criteria for organ donation, critical care management plays a crucial role in optimizing the functional outcome of an organ after donation. Several pathogeneses resulting from brain or cardiac death may be addressed with medication therapy (Rosendale 2003). Brain death may interrupt the hypothalamic-pituitary axis, leading to hormone depletion. Impaired thyroid-stimulating hormone secretion and decreased peripheral conversion of T4 to T3 can lead to progressive decline in cardiac contractility. Hormone supplementation can improve perfusion and maintain aerobic metabolism in tissues. Additionally it can lead to increased blood pressure, left ventricular function, and cardiac output. Administration of high-dose, supraphysiologic triiodothyronine (T3) or thyroxin (T4), an initial bolus followed by an infusion, is recommended.

Steroids can attenuate the effects of proinflammatory cytokines and have been shown to prolong allograft survival. Finally, centrally mediated diabetes insipidus from early depletion of anti-diuretic hormone may lead to hypovolemia, contributing to deleterious hemodynamic instability and electrolyte derangements. Replacing free water losses and use of vasopressin and/or desmopressin can combat these effects (Kotloff 2015; Wood 2004). Table 3-7 lists suggested dosing strategies.

Table 3-7. Medications Used in the Care of Organ Donors

Drug	Dose
Triiodothyronine (T3) or Thyroxin (T4)	4 mcg bolus, start infusion at 3 mcg/hr 20 mcg bolus, start infusion at 10 mcg/hr
Methylprednisolone	15 mg/kg or 1 g given every 12 hours
Vasopressin	0.01–0.04 units/hr[a]
Desmopressinb	1 4 mcg

[a]May be titrated to maintain urine output or hemodynamic goals; higher doses may be used with caution.

[b]May be used for hemodynamically stable patients or in combination with vasopressin to achieve the desired metabolic effects

Information from Kotloff RM, Blosser S, Fulda GJ, et al. Management of the potential organ donor in the ICU: Society of Critical Care medicine/American College of Chest Physicians/Association of Organ Procurement Organizations consensus statement. Critical Care Medicine 2015;43:1291–325.

CONCLUSION

The patient populations discussed in this chapter present with a unique spectrum of medical challenges. Adverse effects and drug interactions associated with immunosuppression should be carefully examined for a potential role in the morbidity of hospitalized patients. For neurologically injured patients, an understanding of cerebral hemodynamics is key to optimizing medical management. These individuals may also benefit from an individualized approach to analgesia and sedation management in the peri-surgical period.

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Self-Assessment Questions

Questions 41 and 42 pertain to the following case.

P.D. is a man being treated for steroid-resistant acute cellular rejection of his pancreas allograft with anti-thymocyte globulin (ATG). This first dose of ATG is being given over 6 hours, with his daily dose of prednisone 5 mg administered just before the infusion. Two hours into the infusion, P.D.'s blood pressure decreases to 70/30 mm Hg and heart rate falls to 52 beats/minute. He is breathing normally but is slow to respond to questions from your emergency response team.

41. Which one of the following is best to recommend first for P.D.?

    A. Slow the ATG infusion rate to deliver the dose over 10 hours instead of 6.
    B. Administer bronchodilators to prevent respiratory distress.
    C. Give intravenous methylprednisolone 1 g immediately to prevent swelling or facial and throat edema.
    D. Infuse 1 L of Ringers' lactate through a large bore peripheral IV over 15 minutes and pause the infusion.

42. Once P.D. is stabilized, you are asked how best to manage his subsequent ATG infusions. Which one of the following is best to recommend for P.D.?

    A. Pre-medicate with acetaminophen, diphenhydramine, and steroids, and subsequent infusions may be run over 4 hours on the general floor.
    B. Pre-medicate with a 500 mL fluid bolus, steroids, and subsequent infusions may be run over 10 hours on the general floor.
    C. Pre-medicate with acetaminophen, diphenhydramine, and steroids, and subsequent infusions may be run over 6 hours with the next dose given in the ICU.
    D. Give no further doses because of the high likelihood this was an anaphylactic reaction, and his allergy list should be updated to include ATG.

43. A patient who received a heart transplant 4 days ago was started on mycophenolate mofetil, tacrolimus, and prednisone. She presents to the ICU with a blood pressure of 144/84 mm Hg (baseline 120/80 mm Hg) and sudden onset of severe headache and blurry vision. Head CT results suggest a diagnosis of PRES, and the blood tacrolimus concentration is 21 ng/mL. Which of the following best describes this patient's treatment considerations?

    A. PRES will likely recur regardless of choice of therapy if the patient becomes hypertensive.
    B. Symptoms of PRES will not reoccur if tacrolimus levels are kept within normal ranges.
    C. The patient now has a strict contraindication to all calcineurin inhibitor (CNI) therapy.
    D. Sirolimus represents a safe alternative to tacrolimus for immunosuppression.

44. Which one of the following patients is most likely to have their postoperative course complicated by a donor-derived infection?

    A. A patient with a prosthetic heart valve receiving a transplant from an IV drug user
    B. A patient on prednisone for treatment of rheumatoid arthritis receiving an allograft from a 28-year-old man treated for syphilis at the age of 24
    C. The recipient of an allograft from a donor with a UTI who received 7 days of appropriate antimicrobial treatment before donation
    D. A patient on dialysis for the past 12 months receiving an allograft from a 63-year-old donor

45. A patient is about to receive a liver allograft from a donor with a known MRSA bacteremia at the time of donation. At your institution, cefotaxime is continued for 48 hours as perioperative antimicrobial prophylaxis in liver recipients, and acyclovir and trimethoprim/sulfamethoxazole at prophylactic doses are started for HSV and PCP, respectively, on postoperative day 5. Which one of the following is best to recommend for treatment of this specific recipient?

    A. Continue routine prophylaxis and perform daily blood culture monitoring for 7 days.
    B. Add vancomycin to be continued for 48 hours postoperatively.
    C. Add vancomycin to be continued for 10 days postoperatively.
    D. Start trimethoprim/sulfamethoxazole on postoperative day 0.

46. A 34-year-old man (weight 60 kg) returns to the ICU after receiving a deceased donor simultaneous kidney-pancreas transplant 20 hours ago for hypoglycemic unawareness and diabetic nephropathy. He has no other significant medical history. Currently his platelets are 297,000/mm^3, hemoglobin 9.2 g/dL, INR 1.0, SCr 6.4 mg/dL, and BUN 113 mg/dL. He has produced 50 mL of urine since the time of transplant. There are no signs of postoperative bleeding, and the surgical team has decided to initiate anticoagulation to prevent pancreatic thrombosis. Which one of the following is best to recommend for this patient?

    A. Warfarin 4 mg orally today, titrated for an INR of 2-3
    B. Enoxaparin 60 mg subcutaneously twice daily
    C. Aspirin 81 mg orally daily
    D. Dalteparin 5,000 units subcutaneously daily

Questions 47 and 48 pertain to the following case.

M.R. is a 39-year-old man with nephropathy secondary to HIV who is undergoing deceased donor kidney transplant after 2 years on the waiting list. He has been on antiretroviral therapy with abacavir 300 mg twice daily, zidovudine 300 mg twice daily, and lopinavir/ritonavir 400/100 mg twice daily for the last 24 weeks. His $CD4^+$ count is 350 cells/mm^3 and he has an undetectable HIV viral load. Because of several antigen mismatches, M.R. is at high risk of allograft rejection. The transplant nephrologist asks for your recommendation about how to approach CNI therapy in M.R.

47. Which of the following is best to recommend for M.R.?

    A. Start tacrolimus 1 mg twice daily and monitor daily trough concentrations.
    B. Start tacrolimus 0. 3 mg every other day and monitor daily trough concentrations.
    C. Start sirolimus to avoid drug interactions between antiretrovirals and CNIs.
    D. Change antiretroviral therapy to avoid drug interactions with CNIs.

48. Which therapeutic substitution is best to recommend for M.R. because of concern for drug interactions with existing antiretroviral therapy?

    A. Use acyclovir in place of valganciclovir for antiviral prophylaxis
    B. Use cyclosporine in place of tacrolimus for immunosuppression
    C. Use oral nystatin in place of fluconazole for antifungal prophylaxis
    D. Use famotidine in place of pantoprazole for acid suppression therapy

49. Which one of the following empiric alterations to a medication regimen is best to recommend in the presence of a drug-drug interaction in an HIV-positive kidney transplant recipient?

    A. Increase the dose of mycophenolate mofetil in a patient starting zidovudine.
    B. Decrease the dose of mycophenolate mofetil in a patient receiving abacavir.
    C. Decrease the starting dose of sirolimus in a patient receiving ritonavir.
    D. Decrease the starting dose of cyclosporine in a patient receiving raltegravir.

50. A 46-year-old woman is admitted to the ICU during a tonic-clonic seizure. After stabilizing the patient, you are awaiting laboratory values and results of her head CT. While evaluating her medical history, you find that she had a liver transplant 3 years ago for cirrhosis secondary to HCV and has been stable on a regimen of mycophenolate mofetil 250 mg orally twice daily, tacrolimus 1 mg orally twice daily, and prednisone 5 mg orally daily. She has recently been diagnosed with recurrent HCV and in clinic earlier this week was started on therapy with ombitasvir/paritaprevir/ritonavir. Her other significant medical history includes hypertension, which in clinic was controlled with hydrochlorothiazide 25 mg orally daily. Her husband states the patient has recently been adherent to her drug regimen. Which one of the following is most likely to be the underlying cause of this patient's seizure?

    A. Hypertensive emergency caused by uncontrolled blood pressure
    B. Previously undiagnosed seizure disorder
    C. Hypoglycemia
    D. Drug-drug interaction between tacrolimus and new protease inhibitor therapy, resulting in tacrolimus toxicity

Questions 51 and 52 pertain to the following case.

G.S. is a 67-year-old man (weight 70 kg) presenting to the ED after suffering spontaneous intracerebral hemorrhage. He has a medical history of hypertension and atrial fibrillation. His home drugs include amlodipine 10 mg daily and warfarin 7. 5 mg daily. His serum sodium is 139 mEq/L, SCr 0. 9 mg/dL, and serum osmolarity 285 mOsm/kg. He has two peripheral intravenous lines that were also inserted on admission. G. S.'s presenting INR is 2.8.

51. Which one of the following would be best to recommend for G.S.'s coagulopathy reversal?

    A. Three units of fresh frozen plasma
    B. Vitamin K 10 mg administered orally
    C. Four-factor prothrombin complex concentrate plus vitamin K 10 mg intravenous
    D. Activated prothrombin complex concentrates plus vitamin K 10 mg intravenous

52. G.S. has an EVD placed to monitor ICP. On day 2 of admission, his ICP increases to 25 mm Hg and remains high for more than 10 minutes after implementing standard measures for treatment of high ICP. Which one of the following is best to recommend for management of G.S.'s high ICP?

    A. 3% hypertonic saline continuous infusion at 70 mL/hour
    B. 23.4% hypertonic saline 30-mL bolus as an intravenous push
    C. 20% mannitol 70 g as an intravenous bolus
    D. 25% mannitol 10 g as intravenous push

53. A 65-year-old woman presents to the ED after falling. She has medical history of hypertension and type 2 diabetes mellitus. Her home drugs include amlodipine 10 mg daily, metformin 1000 mg twice daily and glimepiride 2 mg daily. Her CT scan demonstrates a subdural hemorrhage with a 10-mm midline shift. The patient is admitted to

the neurologic ICU. She is currently NPO while awaiting a burr-hole evacuation of her hematoma. A point-of-care blood glucose measurement is 220 mg/dL (1500); 252 mg/dL (1800) consecutive readings. Basic metabolic panel blood glucose is 282 mg/dL. Which one of the following is best to recommend for management of hyperglycemia in this patient?

A. Restart home metformin 1000 two times a day.
B. Initiate insulin sliding scale.
C. Administer 10 units of insulin glargine at bedtime.
D. Initiate insulin infusion.

54. A 21-year-old man is admitted to the neurologic ICU for management of acute TBI after a skateboarding accident. He is initiated on levetiracetam 1000 mg twice daily for seizure prophylaxis. What is the optimal duration of seizure prophylaxis to recommend for this patient?

A. 3 days
B. 7 days
C. 14 days
D. 21 days

55. A 67-year-old man is admitted to the neurologic ICU for management of subdural hemorrhage after falling at his home. He was obtunded on presentation and was intubated on arrival to the ED. His Glasgow coma scale score on presentation was 8T. An extraventricular drain was placed for monitoring of ICP. Which one of the following is the optimal hemodynamic goal for this patient?

A. Intracranial pressure > 25 mm Hg
B. Cerebral perfusion pressure > 70 mm Hg
C. Mean arterial pressure < 60 mm Hg
D. Systolic blood pressure < 100 mm Hg

56. A 36-year-old woman is admitted to the neurosurgical ICU for management of refractory status epilepticus. She was intubated on arrival to the ED. Her current drugs include: fosphenytoin 200 mg every 12 hours, levetiracetam 1500 mg twice daily, and propofol 50 mcg/kg/min. Which one of the following best describes the therapeutic goal with continuous sedation for the initial 24 hours of therapy in this patient?

A. Maintain light sedation with RASS score of 1 to 2.
B. Maintain moderate sedation 2 to 3 and monitor mental status with neurologic exam and patient's ability to follow directions.
C. Maintain moderate sedation and titrate therapy with daily interruption of sedation.
D. Maintain moderate–deep sedation and titrate therapy based on cEEG and seizure activity.

Questions 57 and 58 pertain to the following case.

A.Z. is a 49-year-old woman admitted to the neurologic ICU after SAH hemorrhage. A CT angiograph demonstrates a difficult-to-treat aneurysm, and the decision is made to place a flow-diverting stent in 1 week.

57. Which one of the following is best to recommend for prevention of rebleeding in A.Z.?

A. Aminocaproic acid
B. Levetiracetam
C. Nimodipine
D. Phenytoin

58. On day 5 post SAH, A.Z. develops acute neurologic deficit demonstrated by increased confusion. A CT perfusion test demonstrates reduced cerebral blood flow near the injury. Her current blood pressure is 138/82 mm Hg. Which one of the following is best to recommend to reduce injury from delayed cerebral ischemia in A.Z.?

A. Reorient the patient to the hospital to reduce confusion
B. Increased ICP to improve cerebral blood flow
C. Increase MAP to improve cerebral blood flow
D. Reduce interruptions to promote sleep and improve cognition

59. Which one of the following represents the optimal periprocedure antibiotic for EVD placement in a patient with history of no known drug allergies and no documented history of resistant bacteria?

A. Ceftriaxone 1 g × 1 dose
B. Vancomycin 1 g × 1 dose
C. Clindamycin 300 mg × 1 dose
D. Cefazolin 1 g × 1 dose

60. A 42-year-old woman is admitted to the neurologic ICU after suffering aneurysmal subarachnoid hemorrhage. An EVD is placed on admission for ICP monitoring and to facilitate CSF drainage. On day 10 of admission, she is diagnosed with ventriculitis. Which one of the following is the best regimen for empiric treatment of ventriculitis in this patient?

A. Ceftriaxone plus vancomycin
B. Ceftriaxone and vancomycin plus ampicillin
C. Cefepime plus vancomycin
D. Cefazolin plus vancomycin

Learner Chapter Evaluation: Perioperative Management: Transplantation And Neurosurgery.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

35. The content of the chapter met my educational needs.
36. The content of the chapter satisfied my expectations.
37. The author presented the chapter content effectively.
38. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
39. The content of the chapter was objective and balanced.
40. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
41. The content of the chapter was useful to me.
42. The teaching and learning methods used in the chapter were effective.
43. The active learning methods used in the chapter were effective.
44. The learning assessment activities used in the chapter were effective.
45. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

46. Apply preventive therapies and design a response to severe adverse effects of immunosuppression in the peri- and post-transplant period.
47. Develop an antimicrobial treatment plan for a transplant recipient whose donor had a confirmed infection.
48. Justify prevention and treatment strategies for post-transplant allograft thrombosis.
49. Design medication adjustments in the setting of significant immunosuppressant drug interactions.
50. Construct therapies to prevent complications such as perioperative epilepsy and postoperative infection in neurosurgical patients.
51. Compose a plan for pre-operative coagulopathy reversal in neurosurgical patients.
52. Assess analgesia and sedation therapies in neurologically injured patients.
53. Design an evidence-based treatment protocol for management of neurologic emergencies.
54. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
55. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 56–58 apply to the entire learning module.

56. How long did it take you to read the instructional materials in this module?
57. How long did it take you to read and answer the assessment questions in this module?
58. Please provide any additional comments you may have regarding this module:

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Title	Release Date	BCCCP Test Deadline	ACPE Test Deadline
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Medication Administration /Critical Care Research	May 16, 2016	September 15, 2016	May 14, 2019
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Cardiology Critical Care	January 17, 2017	May 15, 2017	January 14, 2020
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Neurocritical Care/ ICU Technology	September 15, 2017	January 16, 2018	September 14, 2020
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